BRAIN

A JOURNAL OF NEUROLOGY

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Brain

A Journal of Neurology

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March, 1948

BRAIN

VOL. 71, PART 1.

MICROGLIOMATOSIS.

A Form of Reticulosis Affecting the Brain.

BY

DOROTHY S. RUSSELL, A. H. E. MARSHALL[1] AND F. B. SMITH.

(From the Bernhard Baron Institute, the London Hospital, and the Pathological Department, the Royal Infirmary, Preston.)

The investigations of Ramon y Cajal, Del Río Hortega and many others led to the separation of the interstitial cells of the central nervous system into two groups. The first group, which includes the astrocytes and oligodendroglia cells is considered to be of epiblastic origin; the second, composed of the microglial cells, of mesoblastic origin. Subsequent researches of Hortega and others have shown that the microglia represents the reticulo-endothelial system in the central nervous tissue, having both the general morphology and the special staining reactions of the macrophages throughout the body.

The application of this knowledge to the classification of the tumours of the brain resulted in the recognition of many neoplasms whose histogenesis could be traced to cells of the first group or to their embryological precursors. The existence of tumours, however, which could be ascribed to the microglial cells has been a matter of considerable dispute. The possibility is considered by Bailey (1929) but is dismissed by him as unproven. Since that time several authors, whose work will be discussed later, have published cases purporting to show such lesions. This paper describes a series of seven cases in which focal tumour-like proliferations of cells of microglial type were identified. In four of these cases the lesions were confined to the brain; in the remaining three similar proliferations were also present in other organs, particularly in those that are the main sites of the reticulo-endothelial system. The microscopic features are sufficiently consistent to warrant their description collectively after the clinical and macroscopic notes that follow.

[1]Working with a personal grant from the Medical Research Council.

Clinical and Morbid Anatomical Features of Cases.

Group I. Cases in which Lesions were Confined to the Brain.

Case 1.—J. W., a male aged 47, was admitted to St. Thomas's Hospital on 16.7.45, on account of progressive drowsiness and "mental change" during the past three months. There was no previous or family history that appeared relevant to his condition. On examination he was mentally confused and drowsy. The nervous system otherwise appeared normal. No papillœdema was present and examination of the cranial nerves, sensation, and muscular power and co-ordination revealed no abnormalities. Speech appeared normal. There was diminished air entry and fine crepitations over the bases of both lungs. X-ray examination suggested the presence of bronchiectasis. B.P. 105/80. The cardiovascular system also appeared normal and no abnormality was found in the abdomen. He became progressively comatose and, developing a hyperpyrexia of 106° F., died three days after admission.

Summary of Necropsy.

The following summary was provided by Professor W. G. Barnard:—

Slight excess of fluid in pericardial cavity. Brown flabby myocardium showing no obvious abnormality microscopically. Valves normal. Slight atheroma of coronary vessels. Slight hæmolytic staining of first part of aorta. Mucopurulent tracheitis and bronchitis. Congestion, œdema and patches of bronchopneumonic consolidation at bases of both lungs, confirmed on microscopical examination. Emphysematous change at both apices. Slight passive venous congestion on macroscopic and microscopic examination of liver. Enlarged and very soft spleen, showing congestion and inflammatory hyperplasia only on microscopical examination. Parenchymatous degeneration of kidneys. No abnormality seen in adrenals, pancreas, bladder, prostate or intestines.

Macroscopical examination of brain.—Externally the brain showed some flattening of the convolutions. On section an ill-defined mass (about 2 cm. wide by 2 cm. from above down by 3 cm. from before backwards) of very soft and friable grey granular tissue infiltrated the head of the left caudate nucleus, extended about the supra-optic recess and anterior commissure and conspicuously involved the tuber cinereum. There was an ill-defined lateral extension into the ventro-medial angle of the left lenticular nucleus. Succulent white ependymal thickening was present over the left stria terminalis. No other macroscopic changes were found in the cerebrum, brain-stem, cerebellum or 4th ventricle.

Case 2.—L. R., a female aged 46, was admitted to the London Hospital on 24.10.33, complaining of severe frontal headache with drowsiness and blurred vision, beginning three days before admission. On examination she was found to have bilateral papillœdema, left facial paresis, deviation of the tongue to the left, and slight intention tremor of the upper limbs. The plantar responses were flexor. Ptosis of the right eye developed four days after admission. Neither spleen nor lymph nodes were palpable. Laboratory investigations showed a normal Wassermann reaction in both blood and C.S.F., and a normal blood-count and sedimentation rate. The C.S.F., which showed a yellow tinge, contained 280 mg. per cent of protein with 10 cells per c.mm. of a lymphocytic type. Increasing coma developed and she died six weeks after admission.

Summary of Necropsy (P.M. 519/1933.)

Slight atrophy of heart. Moderate atheroma in coronaries and aorta confirmed microscopically. Congestion of lower lobes of both lungs. Œdema and congestion

of liver. Congestion of kidneys and mucosa of small intestine. Adrenals normal. Body of uterus, cervix and right fallopian tube and ovary absent. Bone-marrow normal. Œdema of spleen showing no abnormality on microscopical examination.

Weights: Brain 1,443 grammes. Heart 295 grammes. Liver 1,230 grammes. Kidneys 224 grammes. Adrenals 13·6 grammes. Thyroid 11 grammes. Thymus 29·2 grammes. Pancreas 68 grammes. Pituitary 0·75 grammes.

Macroscopic examination of brain.—There was moderate flattening of the convolutions, and moderate tonsillar herniation. The basal leptomeninges appeared somewhat opaque. On section an ill-defined homogeneous pinkish-grey granular tumour (5 cm. from before back by 4·7 cm. from above down) enormously expanded the 3rd ventricle, and extended forwards into the anterior part of the fornix and the genu of the corpus callosum, downwards into the hypothalamic region to join and possibly invade the optic chiasm, backwards to the region of red nucleus and quadrigeminal plate, and upwards to the tela choroidea. The tumour lay more to the right side than the left and extended laterally into the inner portion of the right globus pallidus, the right caudate nucleus, the adjacent internal capsule and white matter of the right temporal lobe, and the anterior-inferior part of the right thalamus. The residual cavity of the 3rd ventricle formed a narrow cleft to the left border of the tumour. The left lateral ventricle was greatly, and the right lateral ventricle moderately, dilated. The pineal body appeared normal.

Case 3.—G. M., a male aged 42, was admitted to the London Hospital on 5.11.27, on account of progressive lethargy, headache and frequency of micturition for seven weeks before admission. In the last week the lethargy had become worse and twitchings of the face and incontinence had developed. There was no previous or family history of importance. On examination he was found to have bilateral ptosis, and no reaction of the pupils to light and accommodation. The plantar reflexes were not obtained. No other abnormality was found in the nervous system. No enlarged glands or spleen were felt. The C.S.F. showed no abnormality and the Wassermann reaction in the fluid was negative. The patient passed into deep coma and died two days after admission.

SUMMARY OF NECROPSY. (P.M. 508/1927.)

Moderate atheroma in arch and descending aorta. Œdema and congestion of liver. Enlarged spleen with pattern obscured by red pulp, showing acute inflammatory hyperplasia on microscopic examination. Moderate congestion of stomach and duodenum. Great congestion and œdema of lungs. Purulent bronchitis and microscopic foci of bronchopneumonia in both lower lobes, especially in right lung. Fibrocaseous nodule, and cavity 0·5 cm. diameter, in apex of right lung. Fibrous pleural adhesions over right and left upper lobes. Congestion of kidneys. Adrenals normal. Fatty marrow throughout femur.

Weights: Brain 1,385 grammes. Liver 2,220 grammes. Spleen 280 grammes. Kidneys 287 grammes. Pancreas 114·2 grammes. Pituitary 0·5 grammes. Thyroid 22·5 grammes. Testes 28·4 grammes.

Macroscopic examination of brain.—The leptomeninges were congested. There was considerable internal hydrocephalus. A mass of firm greyish-yellow ill-defined growth (up to 4 cm. wide by 2·5 cm. deep) in the hypothalamus extended bilaterally and symmetrically into the lenticular nucleus and internal capsule. The cavity of the 3rd ventricle was greatly narrowed.

Case 4.—A. E. H. (47/77. Path. Dep., Preston), a girl of 15 years, was admitted to the Royal Infirmary, Preston, on 3.1.47, complaining of headache, drowsiness and difficulty in walking of about one month's duration. Both pupils were con-

tracted, she had bilateral nystagmus and ataxy of the legs and was in a confused, noisy and restless state, with a temperature of 100° F. She had a previous history of polydypsia and polyuria for at least two years, and for four months had frequently fallen asleep at unusual times and places, and had developed an excessive appetite. She also had a history of a copious blood-stained purulent nasal discharge for "years" previously. She was said to be intellectually precocious. There was no physical evidence of puberty. Examination of the C.S.F. on two occasions showed a raised pressure with a total protein of 30 to 60 mg. per cent; chlorides 850 and 900 mg. per cent, and 23 to 30 cells per c.mm. of a lymphocytic type. The Lange curve was 0012232110 and the Wassermann reaction negative. The blood-count was normal. Two remissions occurred in the course of her illness but she developed increasing coma and died four weeks after admission.

Summary of Necropsy.

Necropsy five hours after death. Normal configuration of body. No pubic or axillary hair. Moderate development of breasts. Acute emphysema of lungs with subpleural petechiæ on right side. Areas of early bronchopneumonia in both lungs. Small uterus and ovaries. Liver, kidneys, parathyroids, thymus and adrenals macroscopically and microscopically normal. Inflammatory hyperplasia and hæmopoietic activity of pulp of spleen. Desquamation of epithelium in many acini of thyroid.

Weights: Brain 1,320 grammes. Heart 110 grammes. Liver 920 grammes. Right kidney 58 grammes, left kidney 70 grammes. Spleen 100 grammes. Thyroid 10 grammes. Adrenals 2 and 2·1 grammes. Uterus 13 grammes. Ovaries 0·8 and 0·9 grammes.

Macroscopic examination of brain.—The gyri were slightly flattened. On section ill-defined greyish induration was present in the hypothalamus, and the ependyma in the lateral ventricles was slightly thickened. No hydrocephalus was present. The spinal cord was not examined.

Group II. Cases in Which Lesions were Present in Other Organs in Addition to the Brain.

Case 5.—W. T. (46/1469. Path. Dept., Preston), a male aged 41 years, was admitted to the Royal Infirmary, Preston, on 19.3.46, on account of a history of repeated Jacksonian fits, headache, and the development of increasing coma for five weeks before admission. He had been under treatment for a primary syphilitic infection for ten months before admission, the Wassermann reaction becoming negative three to four months after the initiation of treatment. No secondary manifestations of the disease had been observed. On admission he was in deep coma, with a C.S.F. pressure of 270 mm. The C.S.F. was of normal composition. The Wassermann reaction was negative. Death occurred three days after admission.

Summary of Necropsy.

Necropsy fourteen hours after death. Swollen brain with flattened convolutions. Two spherical yellowish-red nodules of tumour tissue with central necrosis, each about 3 cm. in diameter, were present in the right parietal and left parieto-occipital cortex. A third nodule (0·8 cm. diam.) was present in the sub-cortical white matter in the left temporo-parietal region. A grey and yellow soft circumscribed lesion, measuring 3 by 2 by 1·5 cm., with central necrosis projected from the posterior-mesial border of the lower lobe of the right lung, below and separate from the hilum. No other signs of disease were found in the body.

Case 6.—A. H., a man aged 45, was admitted to the London Hospital on 28.3.39,

with an eight-weeks history of drowsiness, lethargy and anorexia. In the previous four weeks he had developed headache accompanied by diplopia, giddiness and blurred speech. No family history of importance was present. He had been treated for syphilis twenty years previously.

On examination he was found to have papillœdema of the left eye, paresis of the left third and sixth nerves and moderate facial weakness, marked right and left nystagmus, moderate generalized hypotonia and a left intention tremor and dysdiadokokinesis. The plantar reflexes were both extensor. There was a general enlargement of the cervical lymph nodes, the glands being firm, discrete and painless. The liver and spleen were not felt. Examination of the C.S.F., which was under a pressure of 200 mm., revealed a cell count of 25 cells, mainly lymphocytes, and a negative Wassermann reaction. The blood-count was normal. The drowsiness progressively increased and death ensued seven days after admission.

SUMMARY OF NECROPSY (P.M. 124/1939.)

Congestion of myocardium. Moderate general atheroma. Fibrous pleural adhesions over upper lobe of right lung. Considerable congestion of lungs. Purulent bronchitis and nodules of bronchopneumonia in right and left lower lobes. Firm, yellowish-white homogeneous infiltration of upper and middle cervical lymph nodes, measuring up to 2 by 1 cm. No infiltration of tonsils, mediastinal, axillary, abdominal and inguinal glands. Diffuse congestion of liver. Congestion only in pulp in soft red spleen, confirmed on microscopical examination. Congestion of stomach and kidneys. Scars of healed ulcers on anterior and posterior walls of duodenum. No abnormality of suprarenals. Patchy congestion of jejunum and ileum. Fatty marrow with few patches of red marrow in femur.

Weights: Brain 1,623 grammes. Liver 1,786 grammes. Heart 343 grammes. Kidneys 343 grammes. Spleen 196 grammes. Pancreas 75·5 grammes. Thyroid 34·4 grammes. Adrenals 18·7 grammes. Testes 55·2 grammes. Thymus 17·9 grammes. Pituitary 1·075 grammes.

Macroscopic examination of brain.—There was slight milky-white opacity of the leptomeninges. The left auditory nerve was diffusely expanded by greyish-white infiltration and similar, but slighter, infiltration affected the left facial and right auditory nerves, and both trigeminal nerves in the proximal part of their course. On section an ill-defined area of friable pinkish-grey infiltration extended into the right lenticular nucleus and pulvinar. The pineal body was expanded by firm grey tissue ($1{\cdot}5 \times 1{\cdot}5 \times 0{\cdot}7$ cm.). Similar tissue extensively infiltrated the vermis, with additional scattered foci in the deeper white matter (fig. 1), some of which involved the left dentate nucleus. The ependyma of the 4th ventricle was replaced by a layer of grey tissue, up to 0·7 cm. thick, which was noticeably developed in the roof and infiltrated the left brachium conjunctivum. Both lateral ventricles were slightly dilated. No abnormality was found in the spinal cord.

Case 7.—A. S., a female aged 44, was admitted to the London Hospital on 4.1.31, complaining of headache, vomiting and drowsiness of three months' duration. Nine months previously, when an out-patient, an enlarged left cervical lymph node had been removed. The histology of this is discussed later. Several years previous to the development of these symptoms she had complained of frequent severe headaches, and had had a course of deep X-ray therapy over the back of the head. On examination three firm rounded swellings were present over the back of the head, one of 8 cm. diameter and two of 2·5 cm. diameter. They appeared to be attached to the underlying bone. Similar swellings were present over each mastoid region, and in front of the ear on the right side. Bilateral papillœdema, left homonymous

hemianopia, and bilateral ptosis were present. There was nystagmus to the right side. The pupils reacted to light and accommodation. Sensation was diminished on the left side of the body, and all reflexes were diminished on the same side. The plantar reflexes were flexor. *Blood*: Hb. 60 per cent; R.B.C. 4·8 millions. Colour-index 0·68: 6,000 W.B.C. per c.mm., with a normal differential count. She received X-ray therapy resulting in considerable diminution in size of the tumours on the scalp and some improvement in the general cerebral condition. She was discharged after treatment but was readmitted four days later with recurrence of severe headache, vomiting and drowsiness. Renewed X-ray therapy again caused some remission of symptoms but she became progressively comatose and died nine weeks later.

Summary of Necropsy (P.M. 173/1931.)

Nodule (3 × 2 cm.) of soft white tissue in substance of right parotid gland. Cervical and bronchial glands macroscopically normal and right lower cervical glands normal on microscopic examination. Left axillary, abdominal and inguinal glands macroscopically normal. Many round nodules of soft white infiltration (up to 2 cm. diameter) scattered through pulp of considerably enlarged spleen. One similar nodule in cortex of right kidney (fig. 2.). Two soft white nodules present in marrow of upper end of shaft of right femur. Similar areas of infiltration present in bodies of 2nd, 3rd and 5th lumbar vertebræ. Slight atheroma, confirmed microscopically, of aortic arch, becoming greater in descending and abdominal aorta. Congestion, œdema and purulent bronchitis in posterior parts of lungs. Congestion of liver and kidneys.

Weights: Heart 280 grammes. Liver 1,462 grammes. Kidneys 280 grammes. Adrenals 9·2 grammes. Spleen 420 grammes. Thyroid 16·8 grammes. Pancreas 72·3 grammes. Thymus 16·7 grammes. Ovaries 4·5 grammes.

Macroscopic examination of brain.—In the right posterior parietal region the dura was infiltrated by a plaque of firm white granular tissue (10 × 2 cm.) projecting from both inner and outer surfaces (fig. 3). The overlying inner table of the skull was slightly eroded but the diploe was not macroscopically invaded by growth. The outer table of the skull in this region showed a "worm-eaten" area of erosion, about 8 cm. in diameter, overlaid by growth, mostly as a thin layer but reaching a thickness of 1 cm. just behind the ear.

The upper wall of the right transverse sinus was invaded by growth throughout the lateral 3 cm. of its course, the lumen being obliterated throughout a length of 1·3 cm. adjacent to the sigmoid portion. Over the left middle meningeal artery there was a plaque of similar, but yellow, growth measuring 1·7 by 1·3 by 0·1 cm.

The right posterior parietal cerebrum was invaded by rubbery white growth beneath the larger plaque over an area about 5 cm. in diameter and for a depth of up to 1·5 cm. The adjacent white matter was congested and œdematous, containing small cysts up to 0·4 cm. in diameter. The ventricular system was displaced to the left, the lateral ventricles being dilated, especially the left.

Summary of Clinical Features and Macroscopic Necropsy Appearances of the Cases.

With the exception of Case 7 all presented signs and symptoms of a rapidly advancing intracranial tumour. Death ensued in two to three months after the onset of symptoms. In Case 7 the development of masses in the scalp and cervical region preceded cerebral symptoms and

the clinical course was correspondingly protracted. No characteristic symptom complex was produced by the cerebral lesions in the series as a whole, as might be expected from the diverse distribution of the foci. The clinical features of severe hypothalamic disturbance in Case 4 are obviously referable to the infiltration of this region and the neurohypophysis (*see* fig. 16). In two cases the cerebrospinal fluid showed the raised protein commonly seen in intracranial tumours when they abut on the cerebrospinal pathway, and slight increase in the cell count was present in three cases, the cells being predominantly of a lymphocytic type. In Case 7, in which areas of infiltration were present in the marrow, a moderate anæmia of microcytic and hypochromic type was present, but was probably coincidental. In all the other patients the blood picture was normal. At necropsy single or multiple ill-defined areas of infiltration were present either in the cerebrum, basal ganglia, brain-stem or cerebellum. The tumour tissue was usually of a soft, grey-white or yellowish, homogeneous appearance, but sometimes contained areas of hæmorrhage and necrosis or caseation. In the three cases constituting the second group similar infiltrations were also present in various sites including the cervical glands, spleen, kidney, parotid, bone-marrow or lung.

Microscopic Examination.

Methods.—All nervous and other tissues were fixed in 4 per cent formol saline. Paraffin sections were stained with hæmatoxylin and eosin, iron hæmatoxylin and van Gieson's solution and Mallory's phosphotungstic acid hæmatoxylin. Other paraffin sections were stained for reticulin fibrils by Laidlaw's method and the method described by Robb-Smith (1937). Some paraffin sections were stained for microglia by a modified method devised by one of us (A. H. E. M.), which will be described in a later publication. Frozen sections were cut from some of the formol-fixed tissues and impregnated by the Weil-Davenport method for microglia, and by Penfield's modification of the silver carbonate technique for microglia and oligodendroglia.

(1) *The cytology of the lesions in the central nervous system.*—In three cases (Nos. 1, 4, and 6) in which parts of the central nervous system not macroscopically infiltrated with tumour have been examined, it is clear that microscopic foci of cellular proliferation may be present at points remote from the main mass or masses. Their identification is a matter of chance and the sites at which they have been found will be indicated after a description of the principal foci.

In general the cytology of the lesions in the central nervous system presents a remarkably uniform and characteristic picture, although certain variations in the degree of differentiation, and the relative proportions of the proliferating cells, exist in different cases.

Under low-power magnification the areas are ill-defined. Towards the centre the cells are closely aggregated (figs. 4, 12) but at the periphery the infiltration is mainly perivascular, the Virchow-Robin spaces being greatly distended by the reacting cells (fig. 5). At a still greater distance from the centre of the growth a well-marked lymphocytic cuffing of vessels, reminiscent of encephalitis, is present. Mitotic figures are numerous throughout the tumour. Scattered areas of necrosis may occur in the central areas but in general this is not a prominent feature. A vigorous macroglial reaction, with the multiplication of fibrous astrocytes and production of glial fibrils, is present in all cases, this reaction being usually of maximum intensity at the borders of the lesion and in the surrounding cerebral tissue, but in some cases also occurring to a lesser degree in the more central areas.

In sections stained with hæmatoxylin or other nuclear stains, the diffusely intermingled proliferating cells may be classified into five types, not all of which, however, are present in every case. The first two of these types, lymphocytes and plasma cells, need little further description; it is on the remaining three that the whole basis of the interpretation of this group of tumours rests. The first of this latter group of cells possesses a small, oval, round, lobed or twisted nucleus with a well-defined and often wrinkled nuclear membrane, a pale nucleoplasm, and a wide-meshed, moderately dense chromatin net, sometimes containing a single nucleolus. In these cells the nuclear morphology is similar to that of the normal microglia of the brain or of histiocytes elsewhere in the body. In the second type of cell the nucleus is of a similar general pattern but of considerably greater size, presenting a more distended and vesicular appearance. Some of these cells show evidence of phagocytic properties in the presence of engulfed red corpuscles in their cytoplasm. A large number of transitional forms, however, link all the cells of these two types. The third member of this group of cells (fig. 6) which were most numerous in Case 1 of the series, shows a spheroidal oval or lobed nucleus with a dense nuclear margin, two or more nucleoli, a darker nucleoplasm and a heavy chromatin net, in a spheroidal cell body which provides only a narrow rim of cytoplasm surrounding the nucleus. In some of these cells two or three nuclei are present, forming giant cells; the nuclear pattern, however, is similar to those with single nuclei. It is difficult to state whether transitions exist between this third group and the cells of histiocytic type; a few cells, however, could morphologically be interpreted as transitional forms. In the majority of the cases there is little

evidence of any participation by the lymphocytes in the tumour process. In Case 5, however, it appeared that many of the lymphocytes were developing into cells resembling the "polyblasts" occurring in the early stages of inflammation. Such development suggests that a proportion of the tumour elements may be supplied by differentiation of the lymphocytes.

The use of specific silver impregnation techniques for microglia provides much greater insight into the nature of these cell types. Three types of lesion may be recognized by the use of such techniques, and the appearances correlated with those seen in preparations stained by ordinary methods. The first type, which was exemplified by Case 3, shows a proliferation of microglial cells of the mature resting type, both diffusely spread in the cerebral tissue and also often forming dense focal accumulations (fig. 11). Such accumulations can be easily recognized in hæmatoxylin-stained sections by the characteristic type of twisted microglial nucleus (fig. 8). All these cells are deeply impregnated by microglial methods. The affected areas are diffusely infiltrated with lymphocytes and plasma cells which often form cuffs round the larger blood-vessels.

In the second type of lesion, as shown in Case 4, two types of cell are present in different areas of the brain; one type of cell, however, being predominant in any one area. The first cell type (fig. 9) is identical with those seen in Case 3, both diffuse and focal accumulations of cells of the mature microglial type being present, the cells possessing many branching processes impregnated by silver (fig. 10). The second cell type (fig. 7) shows a spheroidal nucleus of greater size, presenting a more distended and vesicular appearance, the chromatin pattern, however, being similar to that of the first cell type. These cells are less intensely impregnated by silver methods and show also less development of their branching processes, thereby approaching more to the amœboid form. A series of transitions may be observed between these two cell types.

The third type of lesion was present in the remainder of the series of cases. In these a smaller proportion of the cells stain by silver methods and resemble resting or amœboid microglial cells (fig. 12), while a further proportion show lesser amounts of silver in their cytoplasm, producing various shades of black and grey (fig. 13). The significance of such feebly impregnated cells will be discussed later.

A variable increase in reticulin fibrils is present in the lesions of this series of cases. In the perivascular infiltrations in the brain the proliferating cells frequently split the normal layers of reticulin surrounding the vessels, without an actual increase in reticulin being present; in the

confluent lesions an increase in fibrils is present in some areas (fig. 14) but in general is not a well-marked feature.

Mention may now be made of the distribution of microscopic foci of proliferation within the nervous system. In Cases 1, 3, 4, 6 and 7, areas of leptomeningeal infiltration by lymphocytic cells were present, both immediately covering areas of tumour in the brain and also in more remote areas. In Case 7, the meninges including the dura and the skull and pericranium overlying the main tumour were diffusely infiltrated by tumour cells. In Case 6 the roots of the 3rd nerves (fig. 15), the pineal gland, and the meninges over the spinal cord and occasional perforating vessels of the cervical cord were similarly infiltrated. In Case 4 microscopic nodules of infiltration were present in the posterior lobe of the pituitary, and doubtless in continuity with the tuberal infiltration, though the pituitary stalk was not examined; these areas were surrounded by a dense zone of lymphocytes and presented a remarkable resemblance to a follicle in a lymph node (fig. 16). Scattered microscopic foci were also present beneath the ependyma of the lateral and 4th ventricles and in the pineal body of this case.

(2) *Lesions in other organs.*—Little separate description is required of the lesions in organs outside the brain. In Case 5 a nodule with a necrotic centre was present in the lung. On microscopical examination the infiltration present at the margin of the necrotic area is composed of cells similar to those in the cerebral tumour (fig. 17), the cells being also impregnated by silver methods. In Case 6, in an enlarged cervical lymph node, numerous follicles of proliferating cells are scattered through the substance of the gland compressing the medullary tissue into narrow cords between them (fig. 18). The cells in such follicles are again of the type present in the brain lesions and many are argyrophil by microglial methods. In methods for the demonstration of reticulin (fig. 19), only a few fibrils penetrate into the zones of proliferating cells, the major part of the reticulin being confined to the strands between the follicular areas. In Case 7 the lymph node removed eighteen months before death (fig. 20) shows a diffuse replacement of the gland tissue by cells which are mainly of histiocytic type, but among which are also cells with larger and more vesicular nuclei and several nucleoli, and also a number of fibroblasts and associated collagen fibres. A nodule present in the bone-marrow of this case (fig. 21) shows also cells of mainly histiocytic morphology, many of which have well-marked lobation of their nuclei, in a few instances giving rise to giant cells. The lesions in the parotid gland, spleen and

kidney of this case are of a similar structure to that in the marrow. A moderate degree of fibrosis is present in the lesions in these areas. The cytology of the proliferating cells in these sites appears identical with that in the tumour in the central nervous system.

Discussion.

A number of cases exist in the literature in which tumours of a type similar to those in our series are described. That of Belezky (1933) appears to be the first recorded example. A case described by Bailey (1926), however, would seem, from the description and illustration, to be of a similar nature although the author considered and rejected this explanation. In both these tumours impregnation of the proliferating cells by microglial methods was obtained. Similar cases were described by Benedek and Juba (1941) in a man of 34, by Awzen (1936) in a girl of 9 years, and by Yuile (1938) in a man of 50. Kinney and Adams (1943) reviewed the previously published cases and contributed two of their own. In all these cases the tumour was confined to the central nervous system. The use of silver techniques for microglia by these authors permits the identification of their cases with those of our own series. A large number of examples, however, exists in the literature of tumours variously described as "peritheliomas," "perithelial sarcoma," "periendothelioma" and "alveolar sarcoma," to mention only a few of the synonyms employed. Reference should be made to the papers of Fried (1926), Abbott and Kernohan (1943) and Hsü (1940) for details of such cases. It would appear from the descriptions and illustrations of these tumours that many of them would fall into the category of microgliomas, but in the absence of specific impregnations of the proliferating cells it is impossible to be sure of this.

It has been stated by some authors (Hsü, Abbott and Kernohan (1943) that tumours described as microgliomas are either gliomas or sarcomas, infiltrated by microglial cells. It is clear that such a view is untenable in the face of the evidence provided by our cases. First the existence of two tumours (Cases 3 and 4) in which the great majority of the cells appeared to be impregnated and which showed proliferation of mature microglial cells at a distance from the main tumour; secondly the presence in three cases of similar lesions in the spleen, lymph nodes and other tissues; and, thirdly, the gradation of intensity in the silver staining of the proliferating cells, provide convincing evidence that these specimens are tumours of reticulo-endothelial elements. Finally the

number and distribution of microglial cells in four examples of secondary tumours of the brain have been observed. Although they form aggregates about foci of hæmorrhage and necrosis they are in general sparse and the appearances are quite dissimilar to those described in this paper.

The term "reticulum-celled sarcoma" has been used by Yuile, and Kinney and Adams to describe proliferations of this reticulo-endothelial type. The usage of this term appears to be based on a confusion in terminology. The term "reticulum" or primitive reticular cell, as used by most authors, describes cells in the lymphoid and splenic tissues which form a syncytial network supported on the reticulin fibrils. These cells are faintly argyrophil when stained by microglial methods and show very feeble storage of vital dyes and of particulate material. It is clear that such cells do not correspond to the microglia of the normal brain, the tissue histiocytes elsewhere in the body or to the cells principally involved in the cerebral tumours of these cases. In many of the described cases, however, including five of this series, a proportion of the tumour cells were only feebly impregnated by microglial methods. From the study of silver preparations in which nuclear staining was obtained in addition to cytoplasmic impregnation, it would appear that the spheroidal cells with several nucleoli and a well-marked chromatin net show little affinity for silver (fig. 13). It might be argued that these cells are the primary elements affected in the proliferation and that the more mature microglial forms represent their differentiated descendants. In this event, since the reticulum cell is the precursor of the histiocyte, such proliferations might correctly be termed reticulum-celled sarcomas. However, as these cells bear little resemblance to the normal reticulum cell of the lymph nodes and spleen, and as in two cases they were not present in the lesions at all, it would appear more correct to adopt the alternative possibility and regard them as an anaplastic form of the mature histiocyte formed in the course of the rapid growth of the tumour. On this view Case 3 of this series may be regarded as a fully differentiated microglioma; Case 4 as fully differentiated except for some foci of atypical cells which, however, still have considerable affinity for silver stains, and the remainder of the cases as showing varying degrees of dedifferentiation. Kinney and Adams also raise the question whether such tumours should be regarded as microgliomas or as sarcoma arising from the histiocytic elements of the vascular pial sheaths. From the material available in this series it would appear that cells of both categories may be involved. Embryologically microglial cells frequently originate from the perivascular sheaths

of perforating vessels in addition to other mesodermal sources; therefore such a distinction is of small value.

From a consideration of our series as a whole it is clear that the proliferative process, whether the central nervous system alone is involved or whether other tissues also are affected, is a variety of that group of diseases now classified as the reticuloses (Robb-Smith, 1938). The lymph-nodes in Case 6 and spleen in Case 7 show that the reticulosis is of the follicular type; in Case 7 all transitions are formed in the spleen between early stages of proliferation in the centres of Malpighian bodies and the nodules seen with the naked eye. The proliferating cells in these extraneural tissues appear to be a mixture of reticulum cells, "prohistiocytes" and histiocytes, the latter being confirmed by silver impregnation. Dr. Robb-Smith, from an examination of the material in Case 6, is in agreement with this interpretation; he considers that "there is a strict analogy between the cells and their differentiation processes in the brain with those of the lymph node" (Personal Communication).

The histological diagnosis of the neurological lesion as part of such a reticulosis presents no difficulty when lymph nodes and other tissues participate, and should indeed be considered clinically when signs of an intracranial tumour are accompanied by other evidence of a reticulosis. If, however, the brain alone is involved, and the lesion appears to be of a solitary character, it may be confused with the so-called "ectopic pinealoma" if the usual stains only are used. This tumour it may be recalled may occur in the infundibular region, brain-stem and cerebellum and is composed of large spheroidal cells with conspicuous nucleoli, together with aggregates of small lymphocytes (Russell, 1944). The distinction between these two conditions, if such exists, lies in the reaction of the tumour cells to microglial impregnation methods; in the "ectopic pinealoma," which is provisionally regarded by us as a form of atypical teratoma, there was no affinity of the cells for silver in the one case available for special examination. Further investigation may show that the so-called "ectopic pinealoma" is a manifestation of the reticuloses. The diagnosis of chronic encephalitis is unlikely to require consideration unless, like Case 4, the infiltration is diffuse and no tumour-like mass is present. But even in Case 4, cytological analysis of the infiltrating cells reveals types that are not recognizable in any of the different known kinds of encephalitis.

Summary.

A series of seven cases of cerebral tumour is described in which the proliferating cells are predominantly of the microglial type. In three

cases the cerebral tumours were associated with lesions of similar histology in other organs. It is considered that the character of the lesions in the brain and other organs justifies the classification of the condition as a reticulosis. The relation of these cases to similar examples in the literature is discussed.

We are indebted to Professor W. G. Barnard for the material and notes on Case 1 of this series, to Dr. T. Foulds and Dr. D. M. Anderson for the clinical information on Case 4, to Dr. R. T. Cooke for the necropsy on this case, and to Mr. John King for the photomicrographs.

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EXPLANATION OF FIGURES.

FIG. 1 (*Case* 6).—Horizontal section of cerebellum and pons showing areas of infiltration.

FIG. 2 (*Case* 7).—Nodule of infiltration in cortex of right kidney.

FIG. 3 (*Case* 7).—View of cerebral hemispheres showing tumour mass extending from the right posterior parietal region to invade and penetrate the dura.

FIG. 4 (*Case* 1).—General view of area of infiltration in the brain. H. & E. ×88.

FIG. 5 (*Case* 1).—Cuffing of cerebral vessel beyond confines of main infiltration by tumour cells and lymphocytes. H. & E. ×115.

FIG. 6 (*Case* 1).—Cytology of cells in infiltration. H. & E. ×1,130.

FIG. 7 (*Case* 4).—Area of proliferation of atypical cells (*see* text). H. & E. ×550.

FIG. 8 (*Case* 3).—Focal proliferation of mature microglial cells. H. & E. ×520.

FIG. 9 (*Case* 4).—Area of dense proliferation of mature microglial cells. H. & E. ×550.

FIG. 10 (*Case* 4).—Area of proliferation of mature microglial cells. Weil-Davenport method. ×280.

FIG. 11 (*Case* 3).—Focal and diffuse proliferation of mature microglial cells. Paraffin silver method. ×280.

FIG. 12 (*Case* 1).—Area of infiltration showing mature microglial cells and less differentiated forms. Paraffin silver method. × 280.

FIG. 13 (*Case* 1).—Mature microglial cells and undifferentiated forms. Paraffin silver method with nuclear counterstaining. × 1,130.

FIG. 14 (*Case* 1).—Reticulin fibrils in cerebral tumour. Robb-Smith's method. × 105.

FIG. 15 (*Case* 6).—Infiltration of oculomotor nerve by tumour cells. H. & E. × 16.

FIG. 16 (*Case* 4).—Nodule of infiltration surrounded by lymphocytes in posterior lobe of pituitary. H. & E. × 80.

FIG. 17 (*Case* 5).—Infiltration in nodule of right lung to show cytological features. H. & E. × 550.

FIG. 18 (*Case* 6).—Centre of cervical lymph node showing the follicular nature of the proliferation. H. & E. × 55.

FIG. 19 (*Case* 6).—Cervical lymph node showing absence of reticulin fibrils from the area of follicular proliferation. Robb-Smith's method. × 105.

FIG. 20 (*Case* 7).—Cervical lymph gland removed a year before death. H. & E. × 390.

FIG. 21 (*Case* 7).—Area of infiltration in bone-marrow. H. & E. × 680.

PLATE I

FIG. 1.

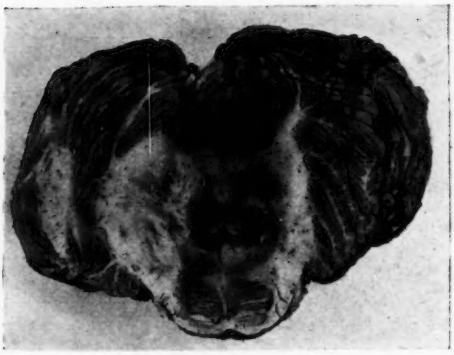

FIG. 2.

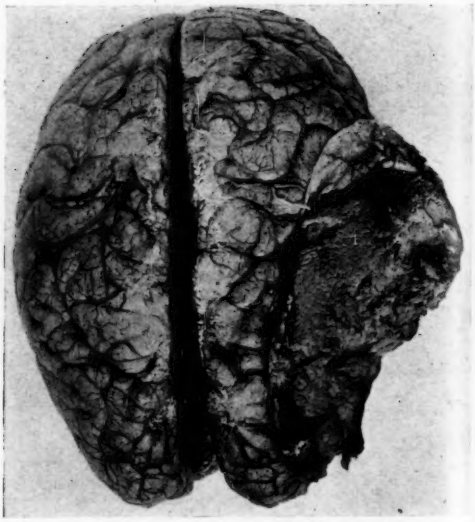

FIG. 3.

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PLATE II

FIG. 4.

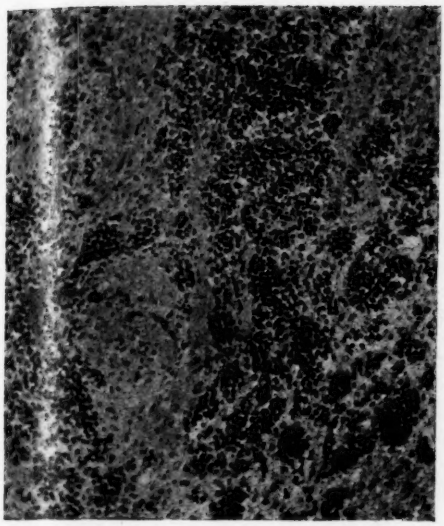
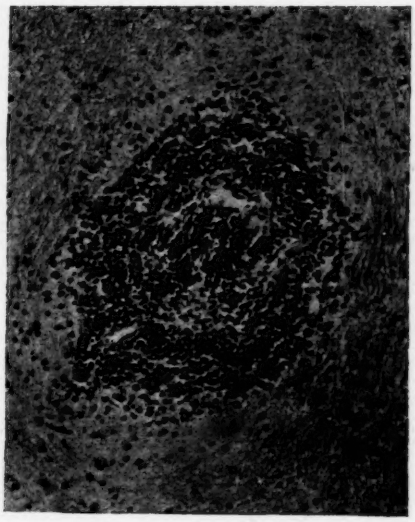
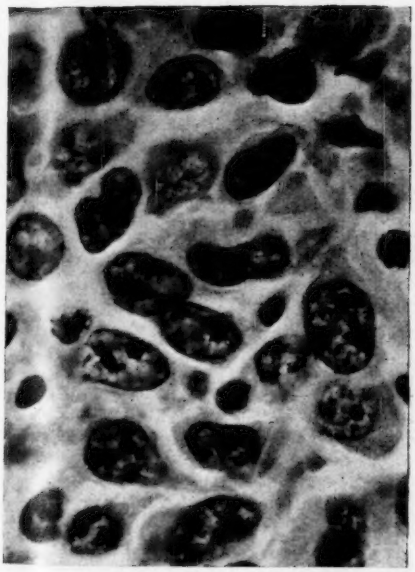


FIG. 5.





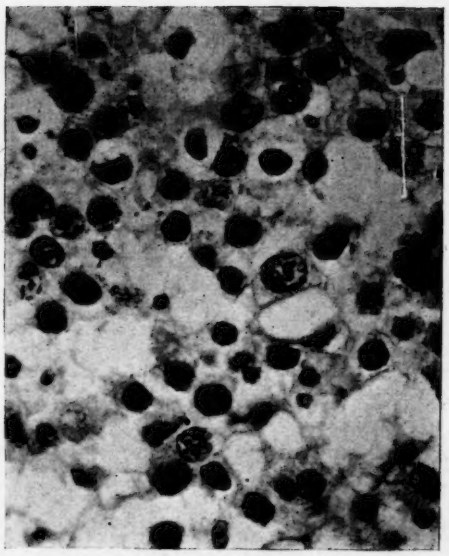


FIG. 6.

FIG. 7.

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PLATE III

FIG. 8.

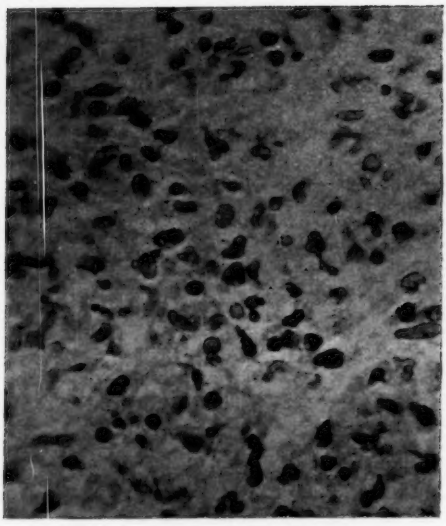
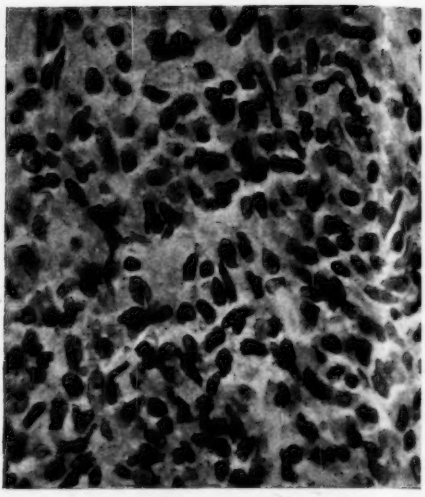
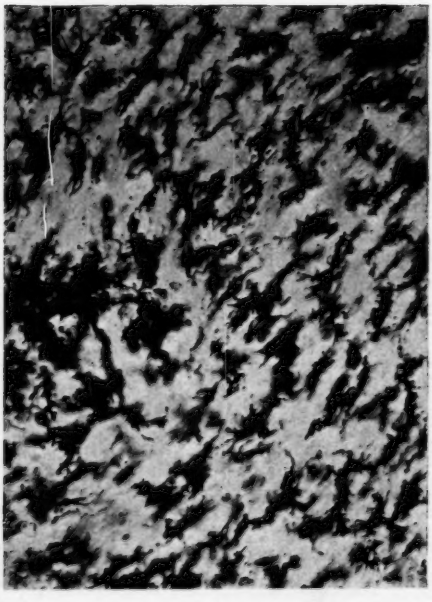


FIG. 9.





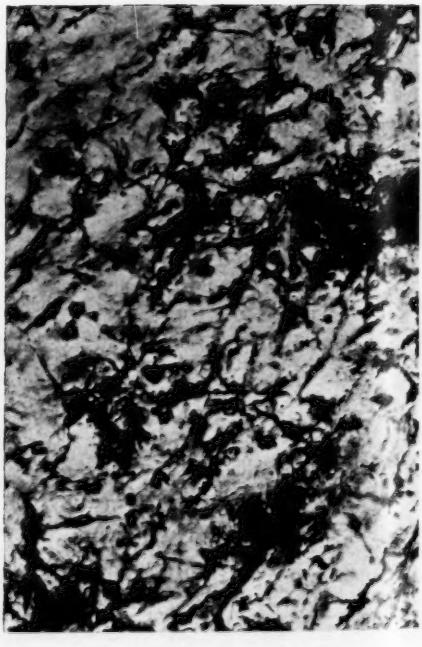


FIG. 10.

FIG. 11.

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PLATE IV

FIG. 12.

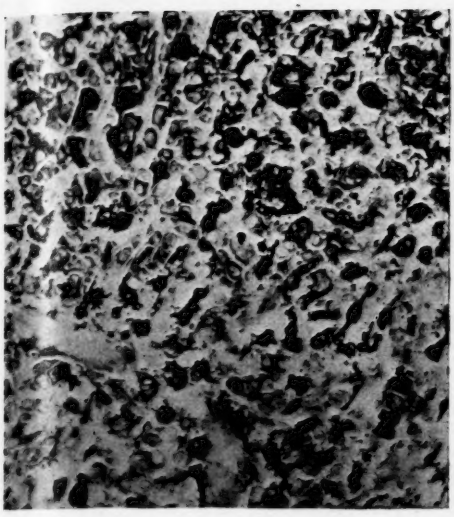

FIG. 13.

FIG. 14.

FIG. 15.

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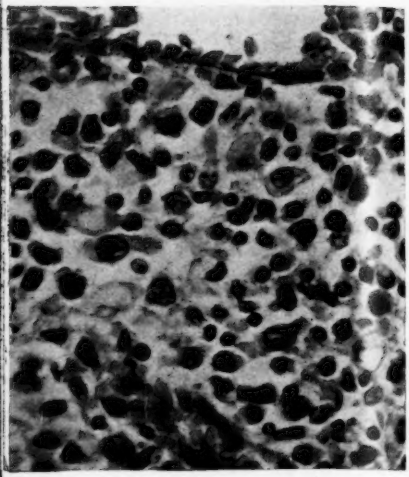
PLATE V

FIG. 16.

FIG. 17.



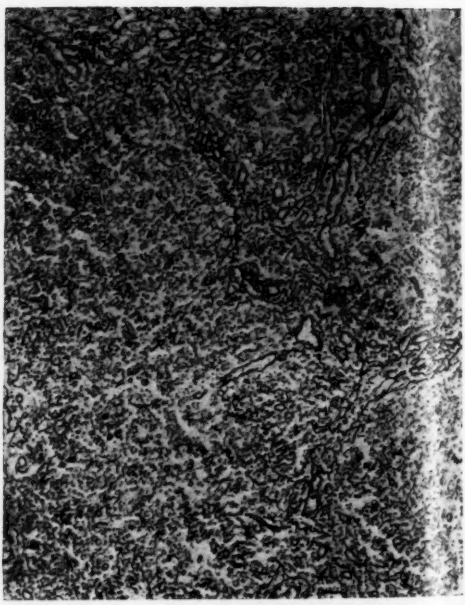


FIG. 18.

FIG. 19.

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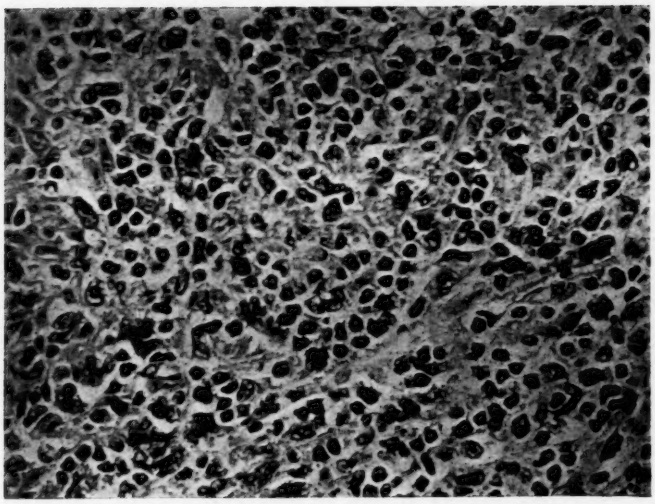
PLATE VI

FIG. 20.



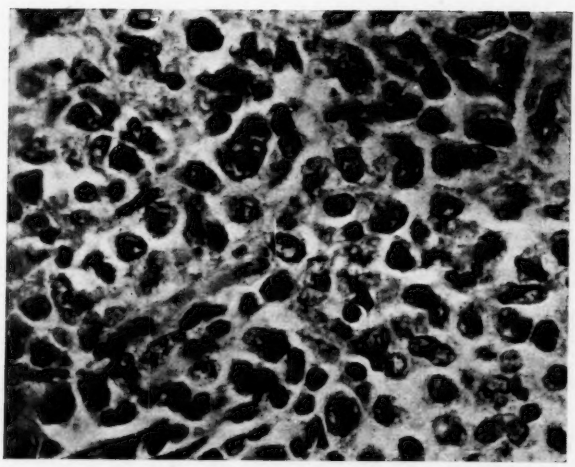


FIG. 21.

To illustrate article by Dorothy S. Russell, A. H. E. Marshall and F. B. Smith.

GUSTATORY SWEATING.

BY

H. A. HAXTON.

(*From the Neurovascular Clinic, Manchester Royal Infirmary.*)

Of the various forms of sweating which may be seen on the face the commoner types are the thermoregulatory and the emotional. So long as they are within limits, these represent normal physiological responses mediated by sympathetic sudomotor fibres. The preganglionic fibres leave the spinal cord in the upper thoracic anterior nerve roots and pass via the corresponding white rami communicantes to the sympathetic chain. They pass upwards and relay in the ganglia, most of them probably in the superior cervical ganglion. The postganglionic fibres join the trigeminal and upper cervical nerves and through these reach the skin.

A third type, gustatory sweating, is something quite different from the commoner varieties. It consists in sweating, accompanied by flushing, in the head and face in response to the stimulus of taste. The foods which provoke it are usually of the spicy or acid type, but it is remarkable that chocolate is frequently found to be the principal excitant. The response appears immediately on tasting the foodstuff and disappears rapidly on cessation of eating; it may be diffuse on the head and face or localized to one part of the face.

Gustatory sweating is not usually seen in normal people, although many have observed it on eating highly spiced foods in hot climates. Occasionally an otherwise normal individual is encountered who exhibits sweating of the face on eating sour or sweet foods. The historic example is Claude Bernard whose response was maximal to chocolate. A similar case was seen in this clinic, the patient showing marked flushing and profuse sweating on eating chocolate. This rare variety, unassociated with any other functional disorder or disease, may be classified as the spontaneous type. It is presumably due to the excessive development of a physiological response to eating which is usually and in most people so slight as to pass unnoticed.

The remaining cases of gustatory sweating may be grouped according to their causative factors, which are:—(1) disease of the central nervous system; (2) local trauma or disease; and (3) sympathetic section.

Disease of the central nervous system.—A diffuse form of gustatory

sweating has been seen occasionally in cases of syringomyelia (Wilson, 1936) and encephalitis (Langenskiold, 1946).

Local trauma or disease.—A localized form of the disorder is not uncommon, and some 90 cases have been published. In these the gustatory sweating has nearly always occurred in the strip of skin in front of the ear supplied by the auriculo-temporal nerve; hence the term "auriculotemporal syndrome" (Frey, 1923). In some cases, however, the sweating area has extended beyond this region, and in others it has been in a different place altogether, for example the submental region (Uprus, Gaylor and Carmichael, 1934; Langenskiold, 1946). Such cases of localized gustatory sweating have followed injury or disease which involved the sensory nerve to the affected part, the usual lesion being a suppurative parotitis. All have the feature that the eating of strongly flavoured foods, particularly acids, results in rapid flushing of the affected zone, followed by perspiration which may be so profuse that sweat runs down the face and causes much embarrassment to the sufferer. Once established, the condition appears to be permanent, and cases of thirty and more years' duration have been reported.

Sympathetic section.—The appearance of this syndrome after operations on the sympathetic nervous system has not often been reported. Guttmann (1931) gave an account of a case in which unilateral gustatory sweating developed on the same side after excision of the whole cervical sympathetic chain. Wilson (1936) reported a case in which the phenomenon appeared on the operated side ten days after a superior cervical ganglionectomy. This case was of additional interest in that a previous section of the trigeminal nerve within the skull had been carried out on the same side. List and Peet (1938) described one case in which gustatory sweating developed after a superior cervical ganglionectomy.

While it has thus been recognized that superior cervical ganglionectomy may be followed by this complication, operations on the sympathetic chain below this level have been generally regarded as immune from this complication, and only one case, mentioned in passing by Lewis (1938), has appeared in the literature. It is surprising, therefore, that in the study reported here gustatory sweating has proved to be a relatively common sequel to upper limb sympathectomy. An attempt has been made to determine the reason for this development, and to correlate it with the appearance of a similar syndrome after trauma or infection in the head and neck, especially in the parotid region.

Results.—In a recent investigation of the late effects of upper limb sympathectomy it was found that out of 12 cases of cervicothoracic

ganglionectomy definite gustatory sweating had developed in 4. The periods between the operations and the onset of the syndrome were one, two, four and nine years. The following case is illustrative:—

E. B., a female bottle-washer aged 27, had a bilateral cervicothoracic ganglionectomy performed in February and April 1933, by Professor Telford, through the posterior approach. The removal on the right side was complete, but the approach on the left side was more difficult and complete removal was doubtful. She was, however, relieved of her severe Raynaud attacks, and remains much improved, although the right hand has shown a slight degree of relapse. The left hand and left side of the face have sweated when she is warm since two years after the operations, while the right side remains dry. She has also noticed that only the left side of the face blushes when she is embarrassed. On the other hand, when she eats cheese or sauce she has a tingling sensation in the right side of the scalp and feels a cold perspiration on the right side of the forehead and face, the right cubital fossa and the palm of the right hand. This syndrome first appeared nine years after the operations.

The pupils are now equal and normal in size, but the ptosis of Horner's syndrome is still obvious on the right side. The hands are cool, the left being slightly moist and the right dry. Strong heating of the body resulted in sweating of the left side of the face, neck, upper thorax and upper limb, but not of the corresponding parts on the right side. The left side of the face became flushed, while the right side remained pale. The skin electrical conductivity was only slightly increased in the right hand by the heating, a finding which indicates markedly subnormal sympathetic activity (Haxton, 1947). Nevertheless, a decided effect was produced by 2 per cent procaine block of the right ulnar nerve at the elbow, the little finger and ulnar border of the hand becoming red and warm, and the electrical conductivity falling to one-tenth of its previous level.

On taking a teaspoonful of sauce the patient rapidly developed a definite flush on the right side of the face and forehead, and within two minutes small beads of sweat could be seen on the upper part of the forehead on the right side. This reaction subsided within two minutes of finishing the sauce. While no colour changes or macroscopic sweating appeared in the right cubital region or palm, the electrical conductivity of the skin in these areas was increased by several times when the sauce was eaten.

A paravertebral block of the right upper thorax with 10 c.c. of 2 per cent procaine resulted in the right hand becoming red and hot, the skin temperature of the fingers rising from 20° to 34° C. The right conjunctiva became reddened and the ptosis was increased. When the block was fully effective, that is ten minutes from the injection, the further consumption of sauce resulted in no vasodilatation or sweating on the right side of the face and forehead, and the tingling sensation was absent. The effect of the block wore off in thirty minutes and the gustatory response returned.

The subcutaneous injection of 13 mg. of pilocarpine nitrate resulted in rapid flushing of the right side of the face and dampness of the right side of the forehead, and a few minutes later a similar response developed on the left side, but the sweating was not so profuse. When the response was well established, further taking of sauce increased the amount of perspiration on the right side, and the tingling sensation was felt by the patient on the right side of the face. The electrical conductivity of the digits of the right hand was increased threefold by the pilocarpine, while no change occurred in that of the left fingers.

Of 24 cases of upper thoracic sympathotomy (the Telford operation) which I personally examined, no less than 9 exhibited gustatory sweating on the face and forehead. The periods between operation and the onset of the sweating varied between a few days and six years, and in fact the cases could be divided into two distinct groups; in 7 the sweating appeared within the first six weeks after operation, and, in the remaining 2, intervals of four and six years elapsed before the syndrome appeared. The principal excitants varied considerably; in 2 cases chocolate and cheese were most effective, in 1 spices and cheese, in 3 hot meals, in 2 vinegar and in 1 pepper. In most of the cases the condition is only very mild in degree, but in 3 it is pronounced enough to cause some embarrassment. The following is a typical example of gustatory sweating following upper thoracic sympathotomy.

I. H., a female cotton-packer aged 16, had bilateral Telford operations in September 1937, for severe hyperidrosis of the hands. Two years afterwards the hands became slightly clammy, and six years after operation she noticed that on eating cheese she felt a hot sensation in the face, which became flushed and started to perspire. This state has continued unchanged, and in the last three months she has noticed that chocolate now provokes a similar response.

When the application of radiant heat to the body had caused pronounced sweating of the trunk, the hands suddenly began to perspire profusely; the forehead showed a trace of perspiration. When the patient ate cheese a rapid flushing of the face and forehead developed, followed within two minutes by sweating of the forehead. The distribution was symmetrical. Paravertebral block of the right upper thoracic region with 10 c.c. of 2 per cent procaine resulted in the hands becoming dry and hot, and in the production of a bilateral Horner's syndrome. Obviously the anæsthetic had spread in the connective tissue anterior to the vertebral bodies to reach the opposite sympathetic chain. Following this block the eating of cheese resulted in no signs or symptoms of the gustatory sweating. When the effect of the block had worn off in forty minutes the gustatory response returned. The subcutaneous injection of 13 mg. of pilocarpine nitrate then resulted in marked flushing and sweating of the face five minutes after the injection, and the sweating was considerably increased by the further consumption of cheese.

Only one case of localized gustatory sweating following injury to the face has been encountered, the details of which are as follows:—

J. H., a female shop assistant aged 20, had been troubled with sweating on eating food, particularly meat and fruits, for five years. The sweating was quite severe, forming drops which ran down her face. The area affected was a small patch on the right side of the face, in the pre-auricular region. This zone had been subject to redness on eating ever since childhood, and there was a small scar in the centre of the region, said to have resulted from a forceps injury at her birth. Section of the right cervical sympathetic chain was carried out just above the middle cervical ganglion, and resulted in a Horner's syndrome. The gustatory sweating, however, continued unchanged, and when she was examined four months later the eating of stewed apples provoked a marked flushing and sweating of the right cheek, extending upwards into the hair line in the cutaneous distribution of the auriculo-temporal nerve, but extending also down-

wards in the territory supplied by the great auricular nerve. Strong heating of the body was carried out at one week and again at four months after the operation, and on both occasions there was thermoregulatory sweating, equal on both sides of the forehead and face. It is obvious, then, that despite the Horner's syndrome, sympathetic denervation of the face on the operated side was incomplete, suggesting the probability of duplication of the cervical sympathetic chain.

Procaine block of the right sympathetic chain in the upper thorax resulted in the abolition of thermoregulatory sweating on the right side of the face, increased injection of the right conjunctiva, evidence of sympathetic paralysis in the right hand and abolition of the gustatory response. The syndrome returned when the effect of the block had worn off.

From these cases, and the literature, the following significant facts emerge:

(1) In unilateral operations, only the operated side develops gustatory sweating.

(2) After bilateral operations, the condition, if unilateral, develops on the side which shows least return of sympathetic activity.

(3) There is a latent period, either of several weeks or of several years, between the operation and the development of the syndrome. In Wilson's case (1936) the latent period was only ten days after superior cervical ganglionectomy.

(4) The condition may develop after interruption of the sympathetic fibres to the face at any level, from below the cervicothoracic ganglion to the postganglionic fibres from the superior cervical ganglion.

(5) Once it is established, there is no evidence that any recovery takes place; on the other hand there seems to be no tendency for the condition to progress in severity.

(6) The syndrome can develop although the trigeminal nerve has been sectioned central to its ganglion (Wilson, 1936).

(7) It can be abolished by the subcutaneous injection of atropine (Wilson, 1936).

(8) It can also be abolished, in the corresponding skin area, by block of the supraorbital nerve (Wilson, 1936).

(9) It is abolished by block of the sympathetic chain in the region of the cervicothoracic ganglion.

(10) There is always evidence of impairment of normal sympathetic activity, for example absent or reduced thermoregulatory sweating, Horner's syndrome in ganglionectomy cases, absence of emotional flushing.

(11) There is excessive sensitivity to mecholine (Wilson, 1936) to acetylcholine (Langenskiold, 1946) and to pilocarpine, and this sensitivity is a

local phenomenon in the skin, since intradermal injections in the affected zone produce an excessive local response (Langenskiold, 1946).

(12) In the localized cases (auriculo-temporal syndrome) there is evidence of impaired function of the cutaneous nerve to the affected area, either hypo- or hyper-æsthesia.

Discussion.

The suggestions which have been put forward to explain this syndrome may be considered. It has been agreed, because of the specific stimulus and rapid response, that the mechanism is by way of a reflex arc, and the afferent pathway is not in doubt; it is provided by the gustatory fibres in the glossopharyngeal and lingual nerves. There is, however, some conflict of view regarding the efferent pathway. The finding that the gustatory syndrome developed after the removal of the cervical sympathetic chain led Guttmann (1931) to suggest that the efferent fibres are accessory sudomotor fibres, not sympathetic in origin and normally inhibited by the sympathetic fibres. Wilson (1936) supported this theory and showed that any accessory fibres which might be present do not leave the brain-stem in the trigeminal nerve. He suggested that the fibres join the trigeminal nerve peripheral to its ganglion. No other anatomical or physiological evidence that such accessory sudomotor fibres exist has, however, been forthcoming, and the fact that the response can be abolished by block of the sympathetic chain in the upper thorax rules out the hypothetical accessory fibres.

List and Peet (1938) believed that gustatory sweating is due to the liberation of acetyl-choline at peripheral, cholinergic, non-sympathetic nerve endings, acting upon the sweat glands, which have become sensitized by the degeneration of their efferent sympathetic fibres. Their conclusion that the cholinergic fibres are non-sympathetic is based on their finding that gustatory sweating on the ipsilateral side of the forehead was present twelve months after superior cervical ganglionectomy in one of their cases, but was abolished two weeks after subsequent section of the supraorbital nerve. In view of the rapidity of sympathetic regeneration, however, and of variations in anatomy which may result in incomplete denervation, they were not justified in assuming that sympathetic activity was absent twelve months after ganglionectomy. Again, the fact that the gustatory syndrome is abolished by sympathetic nerve block in the upper thorax disproves the theory.

We are faced with the paradox that gustatory sweating appears not infrequently after interruption of the sympathetic pathways to the face,

and is most evident in cases in which the recovery from this interruption is most incomplete, and yet it can be abolished by complete interruption of the sympathetic supply to the face and head by block of the chain in the upper thorax. The condition necessary for the development of the syndrome would seem to be minimal sympathetic activity in an area which has been largely deprived of sympathetic innervation.

But gustatory sweating does not develop in every case in which this condition is present. What, then, is the explanation of the apparent susceptibility of some patients to the syndrome? It is most unlikely that the explanation can lie in the regenerating fibres following the wrong pathways, an explanation postulated for the auriculo-temporal syndrome, since the phenomenon is not an abnormal response to the gustatory stimulus but an exaggeration of a normal response which is sufficiently well-marked in some normal individuals to cause symptoms and signs of the gustatory syndrome. The responsible factor is much more probably a sensitivity which develops to chemicals of the cholinergic group. In the case of unilateral gustatory sweating cited here, there is no doubt that such a sensitivity exisited on the affected side, and each of the other cases tested with injections of pilocarpine showed what appeared to be an excessive response on the forehead and face. It seems likely, therefore, that the peripheral mechanism of gustatory sweating is a humoral one, the acetylcholine liberated at the functioning cholinergic sympathetic endings producing excessive activity in the adjacent sensitized de-efferented endings. In cases of superior cervical ganglionectomy the sensitivity is at the cutaneous endings of the degenerated sudomotor fibres, but in cases of thoracic sympathotomy the sensitivity may be in the ganglion cells, since this operation gives an almost complete preganglionic interruption of the sympathetic outflow to the head. There is evidence, however (Ashcroft, 1937), that after preganglionic section the postganglionic sympathetic nerve endings develop a sensitivity of three times normal to the effector chemical. The amount of sensitivity developed appears to differ greatly between cases and the patients whose cholinergic endings become excessively sensitized are those who develop the gustatory syndrome.

The necessary cholinergic sympathetic activity in the skin of the head and face, or in the superior cervical ganglion, may come from regeneration, as in cases in which the syndrome does not appear for several years after operation, or it may be due to incomplete sympathetic denervation of the head and neck by the operation, as in cases in which the syndrome appears within a few days or weeks of sympathetic section. In the case

of the Telford operation, a few sympathetic fibres for the skin of the head and neck may leave the cord in the first thoracic white ramus communicans, which is left intact; in the case of superior cervical ganglionectomy a few fibres may by-pass this ganglion along such vessels as the facial and vertebral arteries. The operation of cervico-thoracic ganglionectomy results in a more complete sympathetic denervation of the head than does the Telford operation. It is significant, therefore, that in the cases developing gustatory sweating, the latent period after ganglionectomy was on an average four years and never less than one year, while after preganglionic section it was less than six weeks in all except 2 of the 9 cases.

Briefly, the view put forward here as an explanation of the gustatory syndrome is that the mechanism is a gustatory reflex, the efferent pathway of which is sympathetic, resulting in the liberation of acetyl-choline at the few functioning cholinergic endings, functioning either through sympathetic regeneration or incomplete interruption, and the excessive response of adjacent sensitized, non-functioning, cholinergic endings to the acetyl-choline.

One fact which cannot at present be reconciled with this theory is that thermoregulatory sweating remains absent or minimal in the affected zone. One would have expected that any intact sympathetic pathways to the skin of the face and head would have reacted to the stimulus of heating the body just as they do to the stimulus of tasting strongly flavoured foods, and that an excessive degree of thermoregulatory sweating would, therefore, develop.

When an irreconcilable factor is present, any hypothesis must be regarded with suspicion, and the explanation given here may have to be modified if further facts come to light.

Auriculo-temporal syndrome.—The localized form of gustatory sweating, or "auriculo-temporal syndrome," has been the subject of considerable study, and several suggestions have been put forward to explain it, including the following:—

(1) Parasympathetic secretory fibres to the parotid salivary gland, running in the auriculo-temporal nerve, regenerate along the wrong neurilemmal sheaths after interruption of the nerve and come to innervate the sympathetic endings in the skin (André-Thomas, 1927; Ford and Woodhall, 1938; Payne, 1940).

(2) The presence of scar tissue in the parotid gland gives rise to excessive tension during parotid activity, and this causes irritation of the sympathetic fibres traversing the gland in the auriculo-temporal nerve (Frey, 1923; Needles, 1936).

(3) The attempts at regeneration of fibres of the auriculo-temporal nerve strangulated by scar tissue in the parotid gland result in abnormal irritability of the cholinergic nerve endings (List and Peet, 1938).

(4) The syndrome is a normally existing reflex deprived of inhibitory fibres by the damage to the nerve supply of the area.

The first three of these theories have the weakness that the response is not always confined to the distribution of the auriculo-temporal nerve, and the fourth is based on a hypothetical mechanism, for the existence of which there is no sound evidence. Langenskiold (1946) has recently ably reviewed the subject; he found that there is a pronounced hypersensitivity to acetyl-choline in the skin of the affected area, and he deduces from this that the local mechanism is a humoral one, the acetyl-choline liberated at cholinergic nerve endings acting on the sensitized autonomic synapses in the skin. The site of liberation of the acetyl-choline is conjectural, but he apparently believes that it is in the salivary gland during its activity, which is a parasympathetic function.

The present study has shown that the acetyl-choline must come from intact sympathetic nerve endings since the response can be stopped by sympathetic block in the upper thorax. This evidence not only deals a further blow at the older theories, but also brings the explanation of the localized gustatory response into line with the diffuse response which may occur after sympathetic section. In both types there is damage of the sympathetic nerve supply to the affected area, with some recovery or retention of sympathetic activity and local sensitivity of sweat glands and vessels to acetyl-choline.

Summary.

(1) The clinical syndrome of gustatory sweating is described and its causes enumerated.

(2) Gustatory sweating has developed in approximately 35 per cent of upper limb sympathectomies in the series investigated, both after ganglionectomy and after preganglionic section.

(3) There is a latent period of either a few weeks or a few years between operation and the onset of the syndrome.

(4) The sweating can be abolished temporarily by procaine infiltration of the region of the cervicothoracic ganglion.

(5) In a single case of localized gustatory sweating following trauma at birth the syndrome could be similarly abolished.

(6) The significance of these observations is discussed in relation to the various theories of the explanation of gustatory sweating and the thesis propounded that the reflex is mediated through sympathetic fibres, fol-

lowing normal pathways, and that the acetyl-choline liberated at the terminations of these fibres produces an excessive response in adjacent, sensitized, cholinergic structures.

I am grateful to Professor E. D. Telford for his helpful advice in the preparation of this paper, and to Professor A. M. Boyd for putting at my disposal the facilities for carrying out the observations.

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THE INFLUENCE OF ALTERATIONS IN POSTURE OF THE LIMBS ON CORTICALLY INDUCED MOVEMENTS.

BY

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R. MAGNUS showed in a series of investigations (1909-1910) that reflexes involving the tail or the extremities could be modified by altering the initial posture of that part of the body which was subjected to reflex stimulation. Thus, it was noted that striking the patellar tendon elicited commonly a contralateral extensor reflex. However, if the contralateral leg was in extension prior to the experiment the stimulation caused then a flexion. This and similar experiments were interpreted to mean that proprioceptive impulses originating in the stretched muscle shunt the reflex into those neurons which were bombarded by proprioceptive impulses.

Although the importance of proprioceptive impulses for the performance of voluntary movements is a common clinical experience the role of proprioception for cortically induced movements does not seem to have been subjected to an experimental analysis.

Method.—The experiments were performed on eight monkeys (*Macacus rhesus*) anæsthetized with "Dial-Urethane" (0·45 c.c./kg. i.p.).[2] A Goodwin stimulator was used to stimulate the motor cortex by means of bipolar silver electrodes placed 2 mm. apart. The frequency was in most experiments 90 per second, the duration of the individual impulse 10 ms.; the intensity of the stimulus was either at threshold or slightly above. The stimulus was applied for five seconds to various cortical foci by means of the Horsley-Clarke apparatus. The animal was in a prone position with the extremities protruding sideways. The uppermost extremities were used since their movement was least interfered with. Prior to the stimulus a joint of the fore- or hind-leg was placed either at an acute or obtuse angle. The cortically induced movement was observed and the activity of the muscles involved was recorded by means of electromyograms, as described earlier (Bosma and Gellhorn, 1945-47). The

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[2] Kindly supplied by the Ciba Pharmaceutical Company.

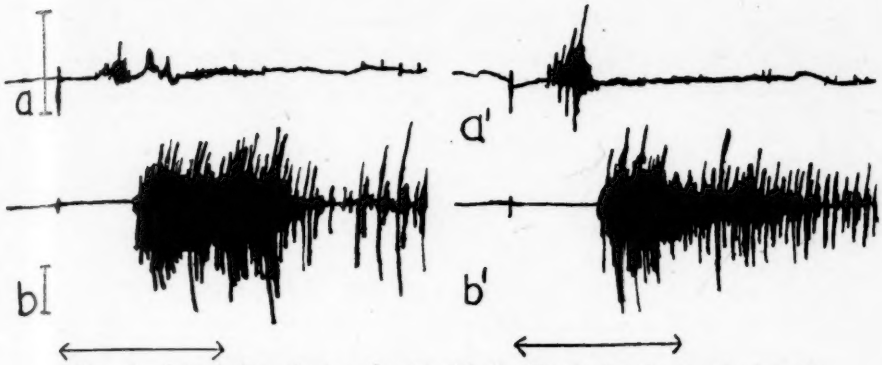

FIG. 1.—Stimulation of site 4[1] with 2·9 V, 90/sec. for 5 seconds (arrow). Calibration = 300 microvolts. Left: knee at 110 degrees, right at 45 degrees. a, a′ quadriceps; b, b′ hamstrings.

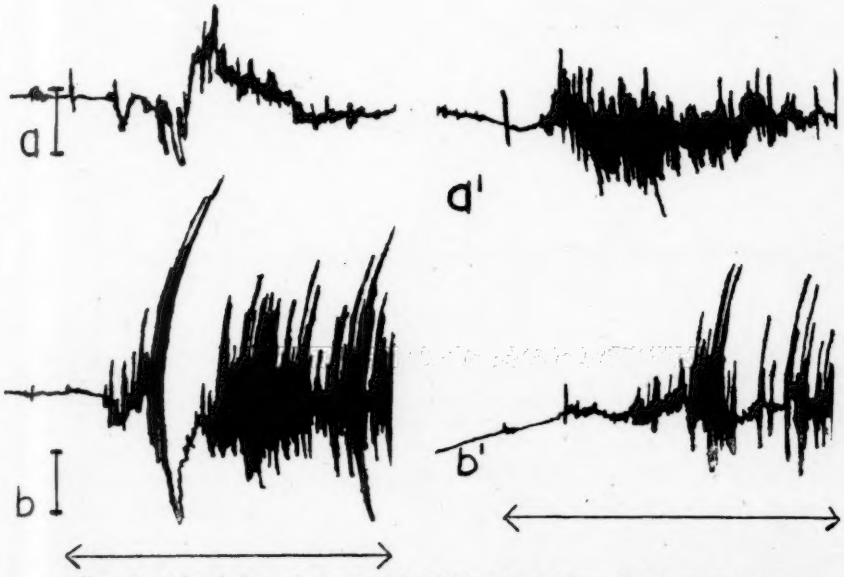

FIG. 2.—Stimulation of site 3—13 with 2·9 V, 90/sec. for 5 seconds (arrow). Calibration = 100 microvolts. Left: knee at 160 degrees, right at 80 degrees. a, a′ quadriceps; b, b′ hamstrings.

[1] The site was measured in these experiments by the co-ordinates of the Horsley-Clarke apparatus, but the numbers given in the legends refer to the schematic drawing of fig. 1 of Bosma and Gellhorn (1947).

individual tests followed each other at intervals of three to four minutes. Each cortical focus was stimulated repeatedly, while the angle of the joint was altered in successive tests.

Results.

In a series of experiments the resting position of an arm or leg was altered and its influence on the effect of the stimulation of the motor cortex was investigated. A typical result is well illustrated in fig. 1. When the leg was placed on the table so that the angle of the knee was 110 degrees the hamstrings responded slightly more and earlier to cortical stimulation than at an angle of 45 degrees. The quadriceps shows the converse result as indicated in the EMGs. Similar but more conspicuous differences are shown in fig. 2, in which by changing the angle of the

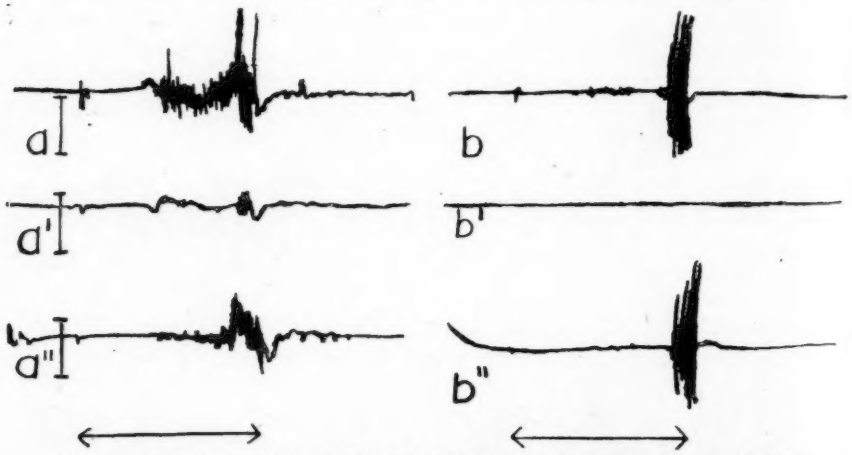

Fig. 3.—Stimulation of site 5 with 2·3 V, 90/sec. for 5 seconds (arrow). Calibration = 100 microvolts. Left: gastrocnemius; right: hamstrings. a, a″ and b and b″ knee at 160 degrees; a′ and b′ knee at 90 degrees.

knee the intensity of activation of the hamstrings and quadriceps could be reversed. Obviously an increase in the initial length of a muscle enhances its responsiveness to a standardized cortical stimulus. In addition, the stimulation caused a contraction of the anterior tibialis and, to a lesser extent, of the gastrocnemius muscle. However, the degree of their contraction as indicated by the amplitude and duration of the EMG was not altered by changing the angle of the knee. In a similar experiment performed on another monkey, alteration of the angle of the knee changed profoundly the response of hamstrings and gastrocnemius

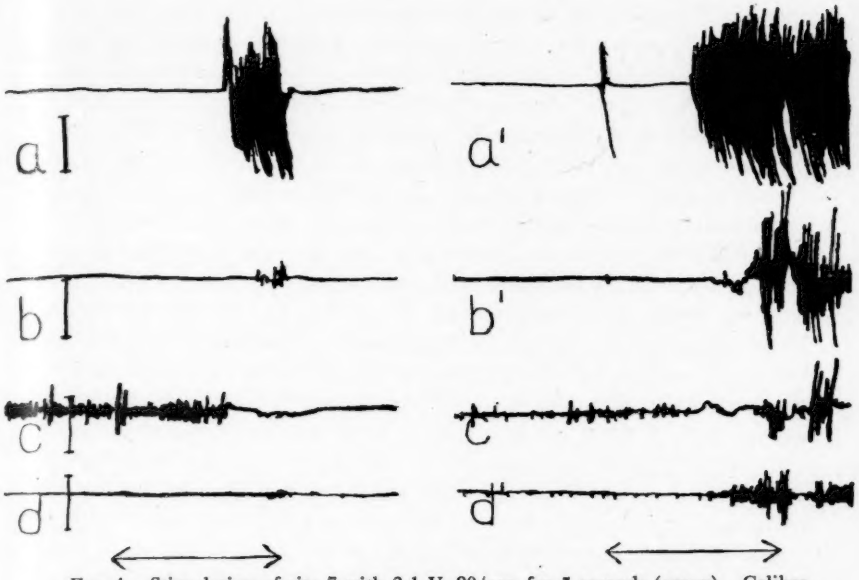

FIG. 4.—Stimulation of site 7 with 2·1 V, 90/sec. for 5 seconds (arrow). Calibration = 100 microvolts. Left: elbow at 45 degrees, right: at 120 degrees. a, a′ extensor carpi radialis; b, b′ flexor carpi radialis; c, c′ triceps; d, d′ biceps.

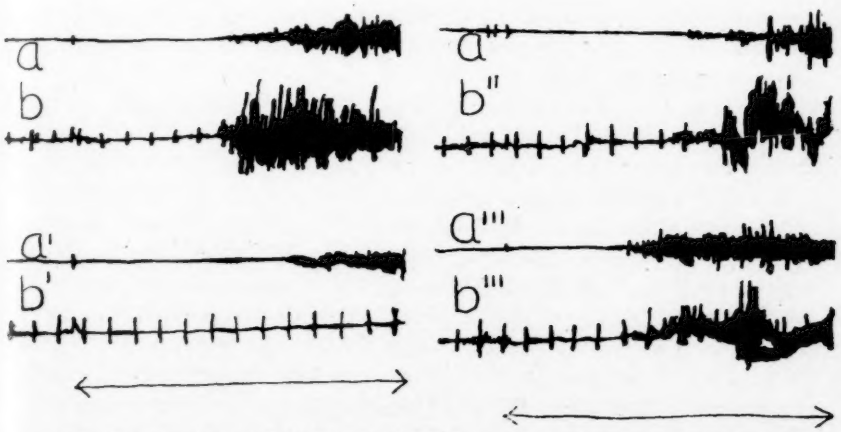

FIG. 5.—Stimulation of site 6 with 3·3 V for a, b, a′, b′ and a″, b″; with 5·5 V for a‴, b‴, 90/sec. for 5 seconds (arrow). a, b, a″, b″: elbow 65 degrees; a′, b′, a‴, b‴ elbow 140 degrees. a to a‴ flexor carpi radialis; b to b‴ triceps.

muscles on stimulation of a site which evoked activity in triceps, hamstrings, and gastrocnemius muscles. The latter muscles (fig. 3) responded at a certain intensity of stimulation when the hamstrings were stretched (angle of the knee 160 degrees), but failed to show a significant reaction with the knee at 90 degrees.

An example illustrating the influence of posture on cortically induced motor responses of the forearm muscles is shown in fig. 4. A flexor point was stimulated with the elbow at 45 degrees and at 120 degrees, while the EMGs of the fore- and upper-arm muscles were recorded. At this intensity of stimulation the biceps reacted when it was in a stretched position; the triceps, however, failed to show activity even when its resting length was increased (angle of the elbow at 45 degrees). At the low intensity used in this experiment the cortical focus elicited activity in the biceps-extensor carpi, the latter muscle showing a greater responsiveness than the former (fig. 4, a′ to d′). When the elbow was placed at an acute angle (fig. 4, a to d) the proprioceptive facilitation of the biceps complex was minimized, and consequently no activity was seen in the biceps, while the EMG of the extensor carpi appeared after a longer summation time and for a shorter duration.

The effect on the triceps complex is determined by the principle of reciprocal innervation (Sherrington) and that of co-innervation (Bosma and Gellhorn, 1945). If we consider first the records obtained under conditions which through proprioception (elbow at 120 degrees) favour the response of the biceps or biceps complex,[1] it is noted that activity appearing in the biceps complex is associated with inhibition of the triceps which, prior to the cortical stimulus, shows slight tonic activity. Following the inhibition of the triceps some slight activity is recorded in this muscle which occurs when the amplitude of the biceps is greatest. This triceps activity as well as that of the flexor carpi is a manifestation of co-innervation. If this interpretation is correct, activity in the triceps complex should be greatly diminished or absent if through proprioceptive conditions the responsiveness of the biceps complex were diminished. Such a conclusion follows from the fact that co-innervation is directly related to the activity of the agonists. Fig. 4, a-d, shows this to be the case. Under proprioceptive conditions minimizing the responsiveness of the biceps complex, co-innervation of triceps and flexor carpi is absent. It is interesting to note that the inhibition of the triceps occurred not only during

[1] That conditions leading to an increased response of the biceps cause greater reactivity in the extensor carpi which forms part of the biceps complex will be shown in a subsequent paper (cf. also Bosma and Gellhorn, 1947).

the activity of the biceps but also when the activity of the biceps complex was restricted to that of the extensor carpi.

An important principle to be explored more fully in a subsequent paper seems to be implicit in this experiment. The proprioceptive conditions favouring the triceps (angle of the elbow at 45 degrees) were ineffective on this muscle and acted only by diminishing the responsiveness of the biceps complex. Apparently changes in position induce proprioceptive facilitation with increasing initial length of the muscle, but this effect depends on the neuronal composition of the cortical focus which is stimulated. Thus, in this experiment proprioceptive impulses originating in the triceps do not reach the cortical neurons which are stimulated. They modify, however, the responsiveness of the neurons in the triceps area, as the following experiment indicates.

The effect of alterations of the angle of the elbow on the reactivity of a cortical triceps focus is illustrated in fig. 5. At 3·3 V. a distinct contraction of the triceps and of the flexor carpi, which is commonly associated with the triceps, is recorded with the elbow at 65 degrees, but no potentials appear in the triceps in response to the same stimulus when the angle of the elbow is 140 degrees (fig. 5, a′, b′). In the latter position the flexor carpi continues to respond to cortical stimulation. When the elbow is returned to the 65 degrees position the original response is obtained again (fig. 5, a″, b″). If, however, the same cortical focus is stimulated with a higher intensity (5·5 V.), action potentials appear in the triceps in spite of the unfavourable position of the elbow (angle at 140 degrees).

The effect of temporal adaptation on the proprioceptive action described in this paper was also investigated. In the experiments discussed thus far the angle of elbow or knee was adjusted a few seconds prior to the application of the stimulus in order to minimize adaptation. It was found, however, that the posture of the leg exerted its typical effects even when the extremities were placed into their final position as long as five minutes prior to the time of cortical stimulation.

In contradistinction to the experiments of Magnus, the overt movement which accompanies cortical stimulation was never changed into its opposite type (e.g. from flexion of the elbow into extension) as the result of an altered position of a joint.

Although numerous experiments proved these results to be valid, it should be mentioned that in some monkeys, possibly due to a variable action of anæsthesia, no distinct effects were elicited on the responsiveness of the motor cortex through variations in the initial position of the

extremities. However, even in these animals typical proprioceptive effects could be demonstrated when their intensity was greatly increased by fixation of one or more joints in a certain position. The results of these experiments will be reported in a subsequent paper.

Discussion.

It was shown that altering the angle of a joint changes the response to cortical stimulation of those muscles which are its movers. The amplitude of the cortically induced EMG of a muscle which is stretched was found to increase with increasing length of the muscle. Thus, the triceps response to a given cortical stimulus is greater when the angle of the elbow is at 45 degrees than when it was at 110 degrees or 160 degrees, whereas the response of the biceps changes in the reverse direction. Similar findings were made on gastrocnemius and tibialis anticus and on the carpal muscles when the position of ankle and hand respectively were changed. The Magnus-von Uexküll rule seems to be valid for cortically induced contractions, although reversal of movement as a result of alteration in position of a joint was never seen.

It is suggested that these changes are due to proprioceptive impulses. The number of discharging afferent nerve fibres as well as their frequency increases with increasing length of the muscle (Matthews) and gives rise to interaction (facilitation) with the cortically induced impulses. Whether this interaction takes place at only the spinal or also at the cortical level remains to be determined.

To take the amplitude of the EMG as an indicator of the strength of the contraction appears to be justified for cortically induced movements. Loofbourrow showed in this laboratory on the isolated tibialis muscle that factors such as frequency or intensity of cortical stimulation which increase the number and frequency of discharging units increase the amplitude of the EMG, whereas it remains constant when, e.g., under conditions of supramaximal indirect stimulation the number of discharging neurons remains unchanged. Moreover, he showed that in experiments with indirect supramaximal stimulation the amplitude of the EMG does not seem to be altered significantly with increasing length of the muscle, whereas this factor is of considerable importance for experiments involving cortical stimulation. Under the latter conditions the amplitude of the EMG increases with increasing initial length of the muscles. The data presented in this paper show the validity of these findings in conditions involving postural changes of the intact extremity.

SUMMARY.

The influence of proprioceptive impulses resulting from postural changes of the limbs on cortically induced movements was studied in the monkey by means of electromyograms. It was found that the Magnus-von Uexküll rule according to which the central excitation has a tendency to flow into the stretched muscle is valid for movements elicited by electrical stimulation of the motor cortex. Thus, from a focus in the lateral part of area 4 which elicits a contraction of the biceps the degree of contraction of this muscle is determined, other conditions being equal, by the initial length of the muscle. Similar results were obtained for triceps, hamstrings, and quadriceps by placing respectively the elbow and knee at acute and obtuse angles while appropriate foci of the cortex were stimulated. However, a reversal of the movement was never accomplished under these conditions.

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OBSERVATIONS ON CUTANEOUS HYPERALGESIA, WITH NOTES ON RELATED REACTIONS.

BY
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Warwick.

IN this paper there are recorded and discussed observations relating to the mechanism of hyperalgesia. In human subjects, areas of cutaneous hyperalgesia several centimetres square may be found surrounding epidermal injuries but a few millimetres square; they begin to develop in from twenty seconds to several hours—usually a few minutes—after the trauma. In the observations here described, such injuries were produced mechanically or by faradism, burning, freezing or intradermal injection of about one-tenth of a minim of benzene, ether, chloroform or alcohol. Skin was considered to be hyperalgesic when pain was aroused by slight pressure, tension, or friction to it. Incidental observations on some related reactions are also presented.

PERIPHERAL NEURAL MECHANISM OF CUTANEOUS HYPERALGESIA AND FLARE.

Sir Thomas Lewis (1936, 1937*a*, *b*, 1942*a*) has studied the production and spread of hyperalgesia produced by minute mechanical or electrical epidermal injuries and by faradization of cutaneous nerves. Mainly from study of the effects of local anæsthetics in such experiments, Lewis concluded that the production and spread of this hyperalgesia is dependent upon a peripheral neural mechanism; flare is subserved by a similar mechanism (Lewis, 1927; Lewis, Harris and Grant, 1927; Lewis, Grant and Marvin, 1927, &c.). I have repeated the relevant experiments, and these conclusions seem inescapable. The effect of local anæsthetic solutions on the production and spread of cutaneous hyperalgesia cannot be emulated by using distilled water or physiological saline solution in similar manner.

THE NERVES CONCERNED.

In human subjects, on four occasions the lateral, and on two the medial cutaneous nerve of the forearm was located by faradic stimulation and anæsthetized by infiltration around it of 2 to 4 c.c. of novocain

in normal saline solution. When anæsthesia of either the medial or the lateral cutaneous nerve of the forearm is complete, on the volar aspect of the limb the respective areas of skin from which no pain can be aroused are approximately 1 cm. smaller than the areas from which no touch sensation can be provoked. The margins of the latter areas coincide within the limits of experimental error. It is presumed that the nerve fibres and endings subserving pain overlap the adjacent nerve's fibres and endings subserving touch for distances of approximately 1 cm. No cutaneous sensation other than pain can be aroused from the area of overlap (Woollard, Weddell and Harpman, 1940).

Crushing a small fold of epidermis, or the intradermal injection of one-tenth of a minim of benzene or chloroform, in the area of skin from which pain only could be aroused, provoked immediate pain which sometimes persisted, and was followed within a few minutes by local reddening, whealing, skin hyperalgesia and flare surrounding and including the site of injury. The area of hyperalgesia was limited, on the side on which the nerve had been anæsthetized, by the margin of the area from which no pain could be aroused. The time intervals between the infliction of the injury and the onset of the delayed reactions recorded varied from half to ten minutes. The sequence in which they occurred was usually that in which they are listed above.

Epidermal injuries, by the methods stated, anywhere in areas rendered anæsthetic and analgesic by regional nerve block resulted in local reddening, whealing and flare of the same degree and extent and at similar time intervals as in normal areas or in areas from which pain only could be aroused. Hyperalgesia and sometimes spontaneous pain were found to be present when analgesia no longer obtained in the injured area.

In one subject, the intra- and subepidermal injection into the forearm of benzene in quantities of up to half a minim resulted in the production of seven ulcers extending into the superficial layers of the dermis. The ulcers and the surrounding skin were not hyperalgesic. From a small area of skin immediately distal to two of these ulcers, pain only could be aroused. In the case of the larger ulcer, the area from which no temperature sensations could be provoked was somewhat larger than the area from which no touch could be aroused, sensitivity to cool being absent from an area somewhat larger than that not sensitive to warmth. Crushing of a fold of epidermis or the intra-epidermal injection of one-tenth of a minim of benzene or chloroform anywhere in the areas from which pain only could be aroused resulted in pain, local reddening, whealing, hyperalgesia and flare. Similar epidermal injuries to normal skin on the same forearm

resulted in similar reactions of approximately the same extent and degree and with more or less the same time relations to the beginning of the experiment. Woollard, Weddell and Harpman (1940), in a clinical and histological study of the innervation of skin surrounding an ulcer produced with carbon dioxide snow in a human subject, found that from a hyperalgesic area of skin immediately distal to the ulcer pain only could be aroused, and that this portion of skin contained only free subepidermal and intrā-epidermal nerve terminals derived from fine nerve fibres. These nerve fibres and endings are similar in type and disposition to those that other observations by these writers and by Weddell (1941) have also shown subserve cutaneous pain. Lewis (1936, 1937*a*) has found that hyperalgesia and flare can occur in the forearms of human subjects on whom stellate ganglionectomies have been performed.

Interneuronal Spread of the Phenomenon Underlying Cutaneous Hyperalgesia and Flare.

The following observations were made repeatedly on two human subjects.

In the abdomen, a small fold of epidermis was crushed, or one-tenth of a minim of benzene was injected intradermally, at a distance of from 8 to 10 mm. from the mid-line. The resulting flare and hyperalgesia involved skin on both sides of the mid-line. One or two minutes more were required for the hyperalgesia and flare to appear and to become fully established on the uninjured than on the injured side of the abdomen. The spread described was prevented by intra- and subepidermal infiltration with aqueous novocain solution along the mid-line.

In the forearm, areas of skin hyperalgesia and flare many centimetres square were produced by minute epidermal injuries in overlap zones of two cutaneous nerves after degeneration of one of them. Woollard, Weddell and Harpman (1940), Weddell, Guttmann and Guttmann (1941) and Weddell (1947) have found histologically that nerve fibres and endings in such zones are separate one from another. In the forearm the area of skin supplied by one neurone subserving pain is probably 1 cm. sq. (Woollard, Weddell and Harpman, 1940; Weddell, 1941), yet an epidermal injury from 2 to 4 mm. sq. may produce there an area of hyperalgesia of 11 × 5 cm.

Faradization of cutaneous nerves may result in the transmission of neural activity to adjacent cutaneous nerves (Foerster, 1925, 1927; Lewis, 1936).

The Relations of Cutaneous Hyperalgesia to Blood and Lymphatic Vessels.

Certain relations between cutaneous hyperalgesia or spontaneous pain and superficial veins have been observed with a frequency and constancy implying that they are not merely accidental. The observations about to be described were made on the forearms of human subjects.

Pain, either present spontaneously in or aroused by friction to or deformation of a hyperalgesia area, is often more severe over cutaneous veins. Superficial veins sometimes clearly delimit hyperalgesic areas of skin. Occasionally areas of cutaneous hyperalgesia are found to extend along superficial veins, either in a distal or in a proximal direction, or both.

When the veins of the forearm are distended and the flow of blood in them is arrested by surrounding the arm with a pneumatic cuff at a pressure of 60 to 70 mm.Hg, after ten seconds to two minutes any skin hyperalgesia present in the forearm commences to increase in severity, especially over distended veins, and spontaneous pain often appears; these effects are more obvious during the first few minutes that the veins are occluded. The whole area of hyperalgesia often becomes somewhat larger, and its extension along superficial veins is almost constant. These effects persist for from a few seconds to several hours after the venous circulation is released, apparently depending on the duration of the occlusion; the maximum time during which the venous circulation was arrested in the experiments in question was fifteen minutes. Leaving the limb dependent has often been observed, after about a quarter of a minute, to lead to spontaneous pain in hyperalgesic areas; this pain disappears, on emptying the veins, after a similar period of time. When the veins are emptied and the pressure in the pneumatic cuff is then rapidly raised from 0 to 130 mm.Hg, thus arresting the arterial blood supply and maintaining the veins collapsed, after about half a minute the hyperalgesia begins to diminish in degree and the area affected becomes smaller. The hyperalgesia usually regains its previous extent and intensity on releasing the circulation. The same results are obtained when the brachial artery alone is occluded. Arterial occlusion while the veins are distended leads to variable results; sometimes the extent and degree of the hyperalgesia are reduced, although not as markedly as when the veins are collapsed; sometimes this reduction is followed by an increase in the degree of the hyperalgesia to its previous intensity; sometimes it becomes more severe. The reactive hyperæmia that follows release of an obstructed arterial supply is sometimes accompanied by a temporary increase in the degree of the hyperalgesia and spontaneous pain may then be experienced.

Trotter and Davies (1909) studied the hyperalgesia that occurs during degeneration and regeneration of cutaneous nerves. It is found mostly in hypoæsthetic skin, is more severe near obvious veins and as its extent lessens becomes more confined to their neighbourhood. They suggested that it is due to a substance produced as the result of division and degeneration of the nerve and escaping only slowly from the affected region.

The relations of cutaneous hyperalgesia to superficial veins have been studied by Lewis and Hess (1933). They produced hyperalgesia by burning, scratching or freezing small areas of skin. Experiments in which the arterial and venous circulations to the limb were impeded alone or in various combinations were carried out. The results were similar, although not identical, to mine. Amongst the conclusions drawn by Lewis and Hess (1933) are that the spontaneous pain and hyperalgesia they described were due to the liberation by injury of a substance, and that the effects of interference with the circulation, and the relations of cutaneous hyperalgesia and spontaneous pain to superficial veins observed by them are explainable by the presence of this substance and by stretching of the skin through engorgement of vessels. Lewis and Zotterman (1926) have found that ultra-violet irradiation and freezing of skin produce vasodilator substances that diffuse through tissue spaces and lymphatics.

Further work (1936, 1937*a*, 1942*a*) has led Lewis to propound the view that, when "nocifensor" reactions such as hyperalgesia and flare are produced through a small cutaneous injury, one or several substances are produced at the site of trauma and that further amounts are produced at a distance from the injury through a peripheral nervous agency. Lewis (1936, 1942*a*) also suggested that the spread of cutaneous hyperalgesia from a small skin lesion is too rapid to be accounted for by the diffusion of a substance; also, the facts that the spread of an area of hyperalgesia is sometimes greater in a distal than in a proximal direction, and that involvement of skin over superficial veins is sometimes on the distal side of the injury were now considered to negative this hypothesis.

The diffusion, through tissue spaces and lymphatic channels, of small amounts of a substance in the deeper layers of the epidermis can be studied by injecting intradermally a small quantity of solution containing a vasoconstrictor substance and determining the spread of the area of blanching. Warming the skin enhances the contrast between blanched and unblanched areas. The present writer has employed quantities of 2 to 7 m. of 1 : 20,000 epinephrine hydrochloride, or 1 to 2 m. of 1 : 1,000 adrenalin hydrochloride, experiments being carried out upon the forearm. The area of blanching begins to increase within a few minutes—sometimes

less than a minute—of injection; at first it surrounds the site of injection in a roughly circular or oval manner, but after about ten minutes it commences and thence proceeds to assume a stellate shape. The processes of the blanched area lie mostly, though not always, over obvious veins. Blanching along lymphatic vessels occurs first in a distal direction and after about thirty minutes or less may reach as far as 6 to 7 cm. from the site of injection. In one series of experiments the circulation was not impeded and the extent of blanching in a proximal direction was determined at given times. In one such experiment, after forty-five minutes the maximum spread of blanching in a proximal direction was 8 cm. from the site of injection. In another series of experiments, the same amount of the same solution was injected intradermally at the same site and the forearm was warmed to the same degree, but the arm was surrounded with a pneumatic cuff at a pressure of 65 to 150 mm.Hg. The arterial systolic pressure of the subjects used was less than 120 mm.Hg. Using the same region as in the example just described, after thirty minutes the maximum spread of the area of blanching, similarly measured, was 9 cm. Such findings were constant and were noted six times. It is concluded that occlusion of veins increases the rate and extent of spread of a substance in the deeper layers of the epidermis of the affected region. If, at previous or subsequent dates to those of the foregoing experiments, a small fold of epidermis be crushed at the same site where the vasoconstrictor substance was or will be injected and the effect of venous occlusion on the resulting area of hyperalgesia be determined, it is found that the area of hyperalgesia often spreads along but one or a few of the veins along which course lymphatic vessels draining the region involved. No spread of the area of hyperalgesia has been observed along lymphatic channels that do not lie over obvious veins. The close relation of lymphatics to blood-vessels, especially veins and capillaries, has been reported by Clark and Clark (1937), Henry (1933), Testut (1929) and others.

The sub- or intradermal injection of a small amount of aqueous adrenalin hydrochloride solution—e.g. ½ to 2 mins. of a 1:1,000 concentration—into an area of cutaneous hyperalgesia results in an increased degree of hyperalgesia in the blanched zone. The more severe area of hyperalgesia increases in size *pari passu* with the development and spread of the zone of blanching within the boundaries of the original region of hyperalgesia. The increase in the degree of hyperalgesia may be such that spontaneous pain is experienced. In some subjects a crush of a small fold of epidermis does not result in an area of hyperalgesia. The sub- or intradermal injection of 1 m. of 1:1,000 aqueous solution of adrenalin

hydrochloride at a site such that the area of blanching includes the crushed skin may then result in hyperalgesia. The sub- or intradermal injection of aqueous atropine sulphate or acetylcholine solutions—amounts employed were 1 to 3 m. containing 1/300—1/100 grain of atropine sulphate and 2 to 5 m. containing 0·03—0·1 gramme of acetylcholine—into an area of hyperalgesic skin results in a diminution in the degree and sometimes in a disappearance of hyperalgesia in the resultant flushed skin. Warming the forearm sufficiently to produce cutaneous vasodilatation, after a few minutes or sometimes slightly less than a minute has similar effects. Cooling the forearm so as to produce vasoconstriction results, after a few minutes, in an increase in the intensity of the hyperalgesia, and sometimes in spontaneous pain. Rivers and Head (1908), in their studies of the sensory phenomena accompanying nerve regeneration, observed that the protopathic state was more pronounced during cold weather. In experiments in which the skin is warmed or cooled, it must be remembered that in a hyperalgesic area the nerve fibres and endings subserving pain present a reduction in threshold to heat and cold as well as to deformation. Thus, for instance, whereas pain is aroused from normal skin when it is heated to 42 to 43° C.—43° C. is the figure given by v. Rein (1925)—subjecting hyperalgesic skin to temperatures of not more than 39° C. in some of the present experiments or even as low as 29° C. in a case described by Lewis and Hess (1933) may arouse pain. This pain comes on after two to three seconds, and may last as long as about half a minute—up to ten seconds is the figure given by Lewis and Hess (1933).

Lewis (1933) has found that in erythromelalgia pain results whenever in the affected region the skin temperature rises to a certain level or the skin is exposed to extreme cold, tension or friction, and that the rise in temperature produced by vascular congestion is sufficient to produce the pain; in Raynaud's disease pain of inflamed fingers may be caused by the quick warming occasioned by a return of blood to them when they are cold; normal fingers present the same phenomenon if the range of temperature change is sufficiently increased. In these conditions he considers that the skin is affected by a substance that lowers the threshold of pain nerve endings to the stimuli mentioned and may result in spontaneous pain being perceived.

Haynes (1932) has shown that histamine and acetylcholine increase, and adrenalin and ephedrine first increase and then decrease the flow of subcutaneous lymph in the dog. Fluid can leak directly from thin-walled veins or blood capillaries into lymphatics (Clark and Clark, 1937).

Related Reactions and Incidental Findings.

Lewis (1936, 1937*a*, 1942*a*, *b*) has discussed interrelations between hyperalgesia, itching, flare, neurogenic urticaria, antidromic vasodilatation, a vascular reaction in response to cold and manifestations of herpes zoster. The following are relevant incidental findings made during my observations, additional to some mentioned in passing elsewhere in this paper.

The longitudinal axes of areas of skin hyperalgesia constantly run parallel to the course of regional cutaneous nerves. When, on either the extensor or the flexor aspect of the forearm, an area of hyperalgesia is large, its longest radius from the site of injury runs distally when the lesion is near the elbow, and proximally when it is near the wrist. Hyperalgesia is more severe at and near the site of the causative trauma.

The periphery of flares observed on the arms and forearms of the subjects on whom the present work was done were either sharply delimited from the surrounding skin or "patchy," small areas showing vasodilatation intermingling with small areas of the same colour as, or paler than, normal skin. The flares were often surrounded by a zone, approximately 1 cm. wide, paler than normal skin.

The areas of hyperalgesia and flare resulting from the same epidermal injury often developed at different rates. The flare often persisted or continued to increase in extent after the area of hyperalgesia was becoming smaller. When both areas were fully developed, there was frequently a close correspondence between their borders. Sometimes either the whole or a part of the area of flare was somewhat larger or smaller than the hyperalgesic area.

When an area of skin, either some hours or even some days after the epidermis had been injured, ceased to be hyperalgesic, it often itched, sometimes for several days. Itching was also sometimes the sole spontaneous sensation experienced in skin surrounding and including a small epidermal injury.

The effects of asphyxia, cooling or local anæsthetics on nerves have been interpreted by Lewis (1937*b*), Bickford (1938) and others as showing that flare, hyperalgesia, pain, tickle and itchy skin and spontaneous itching are mediated by different nerves. It is more probable that the explanation of the findings in question is on more physiological rather than on such anatomical lines. The complexity of the effects of asphyxia and local anæsthetics on nerve are indicated by observations of Sinclair (1947), Feindel (1947), Lewis and Pochin (1938), Gernandt and Zotterman (1946), Heinbecker, Bishop and O'Leary (1934), Zotterman (1933), Granit, Leksell and Skoglund (1944) and others. Simpler factors concerned are the state

of myelination of the nerve fibres and their diameter, and both may vary in different parts of a nerve fibre (Weddell and Harpman, 1940; Bjoerkman and Wohlfart, 1937). I have found that when 2 per cent procaine in physiological saline solution is injected around a cutaneous nerve within the distribution of which there is a hyperalgesic area, slight deformation of or friction to this area arouses pain immediately before and after the introduction of fine sharp steel needles into the epidermis and dermis, the application to the skin of von Frey hairs or a camel-hair brush, bending hairs and application of warmed or cooled metal rods arouse no sensation whatever from the hyperalgesic as well as from the surrounding skin. The time required for the procaine solution to render hyperalgesia no longer detectable is somewhat longer than that required to obtain anæsthesia and analgesia to the stimuli just listed, although hyperalgesia is mediated only by the terminal nerve apparatus subserving pain. Judovich and Bates (1946) found it possible to abolish neuralgia by injecting somatic nerves with an ammonium sulphate solution, pain to pin-prick remaining. During recovery from regional nerve block anæsthesia with procaine in normal saline solution, I have sometimes found a stage at which either warm or cold stimuli are all reported warm; at a later stage, touch stimuli may be reported as tickling. Bickford (1938) has found that tickle, pain, itchy skin and spontaneous itching are all conveyed in the anterolateral tracts of the spinal cord. Foerster and Gagel (1932) and Zotterman (1939) have found that nerve fibres subserving tickling, pain and temperature sensations course together in the spinal cord and midbrain. Zotterman (1939) has found that tickling and itching are subserved by thin afferent nerve fibres, and that increase in stimulation of such fibres alters the sensation described as tickling to itching and burning.

Flare, and perhaps itching, would appear to be mediated by the same anatomical neural system as that subserving hyperalgesia; the release of a substance is also concerned in the production of flare (Lewis, Grant and Marvin, 1927).

The well-known observation that hyperalgesic areas are hypoæsthetic (Trotter and Davies, 1909; Riddoch, 1938; Lewis, 1936, and others) I have confirmed. Zotterman (1939) has presented evidence suggesting that touch impulses probably reach the brain before pain and itching impulses reach the spinal cord, and that the former exert an inhibitory effect upon the latter; a similar explanation has been advanced by Foerster (1927). The observations of Feng (1933) suggest that when the phenomenon in question follows skin injury the liberation of potassium may be concerned. The innervation of at any rate some tactile nerve endings by "accessory" nerve

fibres and terminals of the type that subserve pain (Weddell and Harpman, 1940, and many others quoted by them) and the observation of Tower (1940), Adrian, Cattell and Hoagland (1931) and Cattell and Hoagland (1931) that neural activity anywhere within the terminal nerve apparatus of one neurone spreads to other parts of this apparatus may perhaps also be invoked to explain the co-occurrence of hyperalgesia and hypoæsthesia.

Clinical Observations.

Williams (1945*a*) has described pain syndromes of the head and neck and their cure or relief by the administration of nicotinic acid. I have confirmed his observations in some 30 cases. Williams (1945*a*) explains his findings on a theory of "physical or intrinsic allergy." Headache produced by histamine administration is abolished by vasodilatation brought about by amyl nitrite inhalation or further histamine injections (Pickering, 1933). The value and mode of action of anti-histamine substances and nicotinic acid (Rosenthal and Minard, 1939; Williams, 1945*a*, *b*) in the treatment of some pain syndromes, of histamine in the treatment of migraine and some other headaches (Butler and Thomas, 1945; Horton, 1940; Hansel, 1947 and others quoted by him) and of carbachol (James, 1945) and progesterone in treating migraine requires further investigation; an analogy may be traced with the use of histamine and nicotinic acid in the treatment of Ménière's syndrome (Atkinson, 1942, 1944, 1946; Shelden and Horton, 1940; Horton, 1941; Harris and Moore, 1940; Lillie, Horton and Thornell, 1944; Williams, 1944, 1945*c*; Day, 1946; Rainey, 1943; and others).

There is evidence (*B.M.J.*, 1947) that limb pain in poliomyelitis may be relieved by increasing the vascularity of the affected part.

Rowbotham (1946*a*, *b*) states that he has cured severe migraine by removal of the lower half of the superior cervical ganglion and the cervical sympathetic chain below it, stripping the outer coats of the external, internal and common carotid arteries and division of the external carotid artery. By this operation I relieved from pain a patient whose outer ear was hyperalgesic and spontaneously painful following burning.

The Mechanism of Skin Hyperalgesia and Some Pain Syndromes.

The evidence presented indicates that the development and spread of cutaneous hyperalgesia from skin trauma are dependent upon a peripheral neural mechanism involving the terminal nerve apparatus subserving pain and the liberation or production and diffusion of a substance. The nature

of this substance is problematical. Lewis (1936, 1942*a*) has recorded a series of negative observations regarding it, and adversely criticized observations of Rosenthal and Minard (1939), from which they concluded that the substance in question was histamine; Lewis (1942*a*, *b*) considers itching, flare and neurogenic urticaria to be due to H substance, which in a case of the latter was found to be released by cholinergic nerves; there was an abnormal factor in the patient's skin, which was rendered unusually responsive by some abnormal quality of her blood plasma. I have found that intense hyperalgesia follows intradermal injection of minute quantities of fat solvents, and noted again the well-known clinical observation that application to abraded areas of fatty or greasy substances relieves pain. The phenomena discussed in this paper are probably mainly dependent upon processes occurring at cell membranes.

The observations recorded suggest that the beneficial effects on some pain syndromes of vasodilator procedures may be due to the action of increased blood flow on a causative substance, a conclusion that had already suggested itself to Lewis (1942*a*). The observations of Mayfield and Devine (1945), Doupe, Cullen and Chance (1944), Bingham (1947) and others show that parts affected by causalgia may exhibit either vasoconstriction or vasodilatation, more usually the latter (de Takats, 1943)—the blood flow is then increased (Miller and de Takats, 1942); the pain may be diminished or increased by cooling or warming. The observations recorded and discussed in this paper show that in interpreting the relations of the circulatory system to cutaneous hyperalgesia, temperature, distension and blood and lymph flow all have to be considered. de Takats (1943) considers that sympathectomy relieves causalgic pain, in spite of its increasing vasodilatation, because although it opens the arterioles it constricts the capillaries. Stimulation of the sympathetic nerve supply to a part affected by causalgia may worsen the pain (Doupe *et al.*, 1944), also in the head, although the cervical sympathetic chain contains no afferent nerve fibres (Davis and Pollock, 1932; Cleveland, 1932; Davis, 1946). Doupe *et al.* (1944) further state that sympathectomy abolishes causalgic pain but that vasodilatation otherwise produced does not; they conclude that causalgia is due to some interaction between sympathetic nerve fibres and axones subserving pain. Indirect support for this view is supplied by the findings of Granit, Leksell and Skoglund (1944), Granit and Skoglund (1945) and many others quoted by them, who have shown that when a nerve is cut, crushed or subjected to moderate pressure, the damaged area functions as an "artificial synapse," nerve impulses there being transmitted from one axone to another. The process occurs more readily from motor

to sensory nerve fibres and is impeded by deep narcosis; Adrian (1930) has also shown that the phenomenon can be abolished by removing the sheath of and connective tissue and blood-vessels adhering to the nerve and treating its cut end with novocain. These findings, however, do not explain many of the observations on cutaneous hyperalgesia recorded in this paper.

Causalgia may be relieved by local anæsthetization or section of an affected nerve distal to the causal lesion (Doupe *et al.*, 1944; Livingston, 1943; Mitchell, 1872; Tinel, 1918, and others), and local anæsthetization of the sciatic nerve in diseased intervertebral disc cases distal to the lesion may relieve pain (Judovich and Bates, 1946); these findings are explainable by the peripheral nature of the neural mechanism concerned in the hyperalgesia here discussed. The process in question may, however, also involve the central nervous system (Livingston, 1943; Lewis, 1942*a*; Kellgren, 1937-8; and others).

The relief of migraine by sympathectomy is probably due to the abolition of vascular spasm (Rowbotham, 1946*a*, *b*, 1942).

Summary.

Observations on cutaneous hyperalgesia following epidermal trauma are presented and discussed.

It has been confirmed that such hyperalgesia is dependent upon a peripheral neural mechanism (Lewis, 1936, 1937*a*, *b*, 1942*a*) involving the nerve fibres and endings subserving pain (Woollard, Weddell and Harpman, 1940).

It has been shown that there is a peripheral interneuronal spread of the phenomenon underlying skin hyperalgesia and flare. Relations of skin hyperalgesia to superficial veins, vasodilatation, vasoconstriction and circulatory arrest have been described and correlated with observations on the spread through tissue spaces and lymphatics of adrenalin injected intradermally and the effects of circulatory arrest on this spread. Interpretation of the relations of the circulatory system to cutaneous hyperalgesia involves consideration of temperature, distension through vascular engorgement and blood and lymph flow. It is concluded that the production or liberation and the spread of a substance are also concerned in the mechanism of the hyperalgesia in question, amplifying observations of Trotter and Davies (1909), Lewis (1936, 1937*a*, 1942*a*), Lewis and Hess (1933) and others.

Some clinico-physiological implications of these findings have been discussed, as have also the related reactions, flare, itching and hypoæsthesia.

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ON THE CENTRAL MECHANISM OF SOME OPTIC REACTIONS.

BY

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THE central mechanism of optic reactions has rarely been the subject of experimental investigation. One of the reasons is that optic reactions and phenomena are often considered merely as results of psychic activity, and therefore to be accounted for by psychological factors. Another reason is that the great majority of the optic reactions are so extraordinarily complicated. The four following reactions, which seemed to be the least complicated, were investigated:

I.—The blinking reflex elicited by a threatening movement, by the sudden unexpected approach of an object near the eye.

II.—The conjugate ocular movements excited by optic stimulation.

III.—The optic placing reactions of the forelegs.

IV.—Optical nystagmus.

The experiments concerning the first three reactions were performed on dogs, while the mechanism of the fourth reaction was studied in pigeons, rabbits, cats, dogs, and monkeys (macacus rhesus).

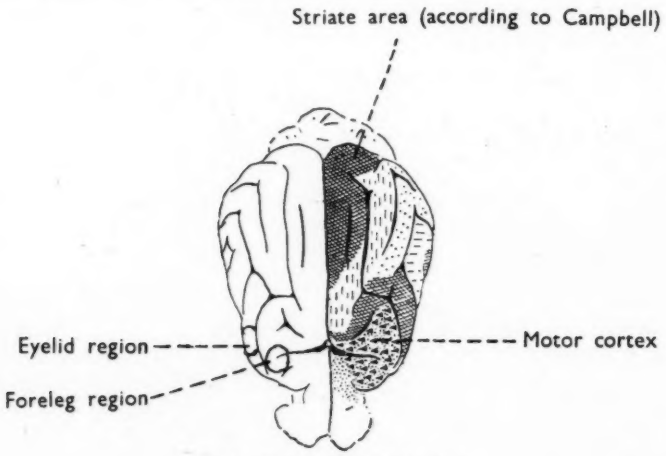

FIG. 1.—Fore-brain of the dog.

I.—THE BLINKING REFLEX.

The blinking reflex excited by touching the cornea or the eyelids, and the blinking reflex elicited by a bright light are subcortical reactions,

whereas the blinking reflex brought about by a menacing movement is a cerebral reaction. The former two still occur, the last is abolished after the removal of both cerebral hemispheres. After the extirpation of the *right* cerebral hemisphere only the blinking reflex brought about by the sudden approach of an object in the *left* half of the visual field is abolished. It is, however, not necessary to remove the whole hemisphere, for the reflex is abolished,

(1) by the removal of the right striate area, and

(2) by free extirpation of the eyelid region of the right motor cortex. The eyelid region is that part of the motor cortex which brings about the closing of the eyelids of both eyes when it is electrically stimulated. This region with surrounding cortex, that is to say the whole sulcus coronarius, must be removed.

(3) After the transection of the cortex of the parietal lobe between the striate area and the motor cortex.

The unilateral disappearance of the reflex after removal of the right striate area can be due to the ensuing left-sided hemianopia, while the absence after destruction of the eyelid region of the motor cortex can be explained by a partial supranuclear facial palsy. The third lesion, the transection of the cortex of the parietal lobe, entails no visual disturbances nor partial facial palsy, but still produces loss of the blinking reflex.

To bring about the disappearance of the reflex it is not even necessary to remove the whole striate area, the removal of only the caudal part has the same effect, *whereas the reflex still occurs when the whole rostral and medial part of the striate area has been removed and only the small lateral-caudal part is spared.*

It is obvious from these observations that the reflex path of the blinking reflex elicited by a sudden threatening movement in the left visual field is as follows: right half of the left retina—right optic tract—lateral-caudal part of the right striate area—eyelid region of the right motor cortex—nuclei of the 7th nerves—muscles of the lids of both eyes (fig. 2).

In collaboration with Raymond Garcin one of us examined at the Salpêtrière in Paris 4 patients with asymmetric blinking reflexes. In all 4 cases the blinking reflex could be excited by a menacing movement in one-half of the visual field, but not by the same movement in the other half; there was no hemianopia and no other disturbances of vision, nor the slightest sign of facial palsy. The blinking reflexes elicited by touching the cornea, the conjunctiva, the eyelids or the lashes, and also the blinking reflex excited by bright light occurred on both sides. It is evident from these results that in human subjects too the blinking reflex elicited

by the sudden movement of an object towards the eye can be abolished without the simultaneous occurrence of hemianopia and without a simultaneous partial facial palsy. As has been verified by operation, one of these patients was suffering from a tuberculoma, another from a meningioma, and the two remaining from a cystic glioma, all located in the

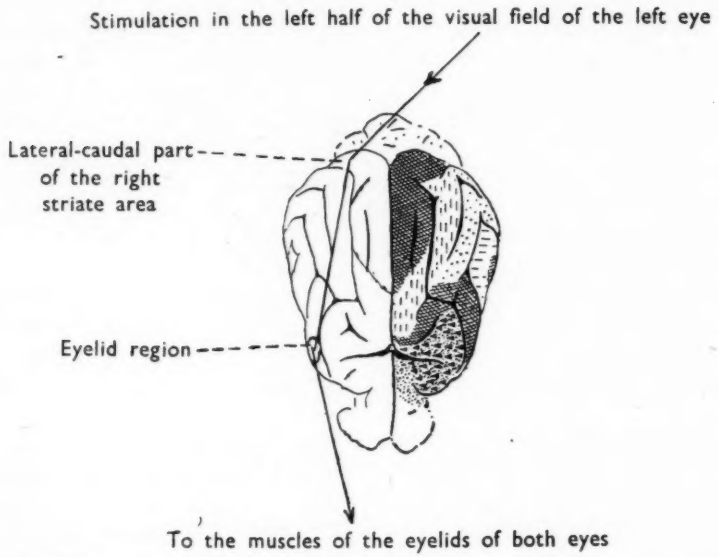
Stimulation in the left half of the visual field of the left eye
Lateral-caudal part of the right striate area
Eyelid region
To the muscles of the eyelids of both eyes

FIG. 2.—Reflex path of the blinking reflex elicited by a menacing movement in the left half of the field of vision.

parietal lobe behind the Rolandio fissure, thus between the striate area and the eyelid region of the motor cortex. The striking accordance between these observations in man and those in animals is evident.

Borowski has studied 114 cases of hemiplegia. In 43 cases the blinking reflex brought about by a menacing movement at the hemiplegic side was abolished; there was no hemianopia, and the corneal and conjunctival reflexes occurred on both sides.

In the other 71 cases the blinking reflexes were all unimpaired. It seems, therefore, that in these cases the eyelid region of the motor cortex and the pathway from this region to the nuclei of the 7th nerves were undamaged.

II. THE OPTIC CONJUGATE OCULAR MOVEMENTS.

The only reactions which occur on electrical stimulation of the striate area are conjugate movements of the eyes. On stimulation of the mesial side of the medial-caudal part of the right area striata the eyes deviate to

the left, while on stimulating the left striate area they deviate to the right. Sometimes, instead of the deviation nystagmus to the right occurs.

This indicates the existence of a special relation between the medial-caudal part of the striate area and the ocular muscles, and it seems therefore that this part of the visual cortex has not only a sensory, but also a motor function. Furthermore it indicates that the pathway which conducts impulses from the striate area to the ocular muscles is not interrupted by many synapses, but that it is a more or less direct one like the pathway (the cerebrospinal tract) from the motor cortex to the anterior horn cells. These conclusions were confirmed by our investigations, which have established that the conjugate ocular movements excited by optic stimuli are abolished after the removal of the whole caudal part, *whereas they still occur after the extirpation of the lateral-caudal and also after the removal of the rostral part of the visual cortex!*

The absence of these reactions can best be observed, when the removal of the caudal part of the visual cortex is combined with a bilateral destruction of the internal ears, so that the animal is also deaf. The conjugate movements of the eyes are then no longer excited either by acoustic or by optic stimuli. Hence the animal always remains staring, and it makes therefore, the impression of being blind.

Moreover it was established that the optic conjugate ocular movements are not abolished by the bilateral ablation of the whole motor cortex. This demonstrates that the optic impulses, which bring about these movements, do not pass through the motor cortex, but are conducted along a more direct way to the oculo-motor nuclei. It seems to be likely that the pathway of these impulses passes through the superior colliculi; conjugate ocular movements also to be produced by electrical stimulation of these colliculi. It follows from these observations, that the conjugate ocular movements elicited by optic stimuli are cerebral reactions and that the impulses, which bring about the conjugate movements to the right are conducted along the following pathway: left half of both retinæ—left optic tract—*medial-caudal part* of left striate area—superior colliculus?—pontine supranuclear oculo-motor centre?—motor nerve cells of the right external rectus (nucleus of nerve VI) and of the left internal rectus (nucleus of nerve III).

III. The Optic Placing Reactions.

If a dog is held in the air and then is brought at a short distance from a table, it can be observed that both legs are moved forward and placed on the table if the latter is in front of the head. On approaching the table with the right side of the head only the right forelimb reacts and is placed

by a sideward movement on the table, whereas the approach with the left side brings about the placing reaction of the left limb only.

If the table stands in the left half of the field of vision and the placing reaction of the left forelimb is hampered by taking hold of this limb with a hand then, instead of the left, the right forelimb is placed on the table, whereby it crosses the left one (fig. 3: II). These optic placing reactions are too *cerebral* reactions. They are abolished: (1) after the removal of both cerebral hemispheres, (2) after ample bilateral destruction of the foreleg region of the motor cortex (that is to say after the bilateral removal of the whole gyrus sigmoideus), (3) after the bilateral extirpation of the striate area.

But, in order to abolish the optic placing reactions, it is again not necessary to remove the whole visual cortex, these reactions being also abolished, if the rostral part of the striate area has amply (thus with most of the adjacent caudal-medial part) been removed, *whereas they still occur when the whole caudal part is removed and only a small rostral part of the visual cortex has been spared*! (fig. 3: I).

It is evident from these observations, that the rostral part of the striate area is of special importance for the occurrence of the optic placing reactions.

The placing reaction of the left forelimb elicited by optic stimulation in the left half of the visual field is abolished after the removal of the rostral part of the right visual cortex, and also after the extirpation of the foreleg region of the right motor cortex. It seems therefore that the optic impulses which produce the optic placing reaction of the left foreleg are conveyed from the right half of both retinæ by the right optic tract to the rostral part of the right striate area, thereon to the foreleg region of the right motor cortex, wherefrom they descend in the cerebrospinal tract to the anterior horn cells of the opposite side, which transmit the impulses through the motor nerves to the muscles of the left foreleg (fig. 3, I).

Although the removal of the right visual cortex, and the destruction of the foreleg region of the right motor cortex both entail the abolition of the optic placing reaction of the left forelimb, the disturbances of the placing reactions after these two injuries are not the same. If a dog wherein the right visual cortex has been removed, is brought with its left side near a table, then no placing reactions at all occur and none of its forelimbs react, whereas after the extirpation of the foreleg region of the right motor cortex, the circumstances being otherwise the same, the right, instead of the left foreleg reacts and is placed on the table (fig. 3, II), whereby it crosses the left one. The animal reacts then as if its left forelimb is being held.

From the observation that optic reactions are no more elicited by optic stimulation in the left half of the visual field after the removal of

the right visual cortex, it appears that the optic impulses produced by this stimulation are conveyed exclusively to the right striate area. From this area they are usually conducted to the foreleg region of the right motor cortex, but under special conditions they can be conveyed to the foreleg region of the opposite side (fig. 3, II).

From the results of these experiments concerning the central mechanism of the optic blinking reflexes, the optic conjugate ocular movements, and the optic placing reactions, it is obvious that a special relation exists

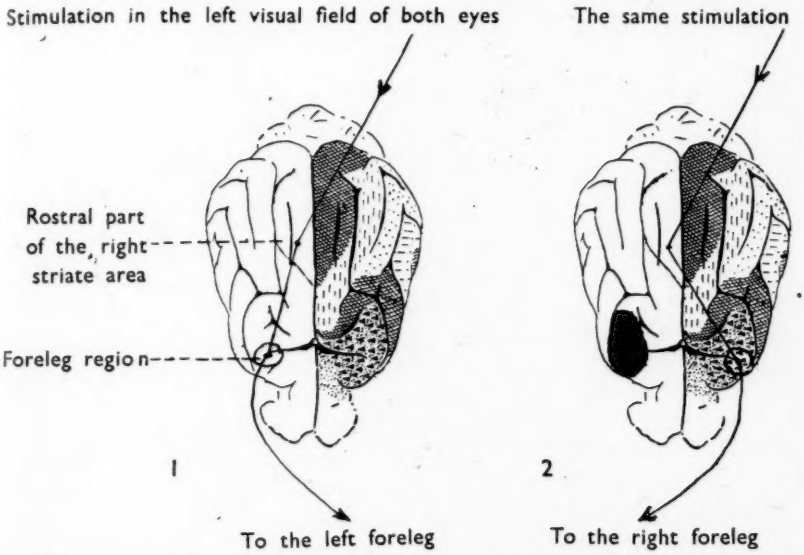

FIG. 3.—I.—Pathway of the optic impulses producing the optic placing reaction of the *left* foreleg, elicited by optic stimulation in the left half of the visual field. II.—Pathway of the optic impulses elicited by the same stimulation and producing the optic placing reaction of the *right* forelimb, the foreleg region of the right motor cortex being removed. This also occurs in normal dogs if the left forelimb is fixed passively.

between: (1) the lateral-caudal part of the visual cortex and the muscles of the eyelids, (2) the medial-caudal part of the visual cortex and the external ocular muscles, (3) the rostral part of the visual cortex and the muscles of the forelimbs.

It seems, therefore, that not only in the motor cortex, but also in the visual cortex of the dog a motor localization exists and that in this part

of the cortex can be distinguished an eyelid region, an eyeball region and a foreleg region (fig. 4).

This does not mean that, for instance, the eyelid region is emerging impulses exclusively to the muscles of the eyelids, nor that these muscles receive impulses exclusively from this and not from other parts of the visual cortex, but only: (1) that the optic blinking reflexes still occur, when the small lateral-caudal part of the visual cortex has been spared, whereas the removal of the whole caudal part entails their abolition; (2) that the optic conjugate ocular movements are likewise abolished after the removal

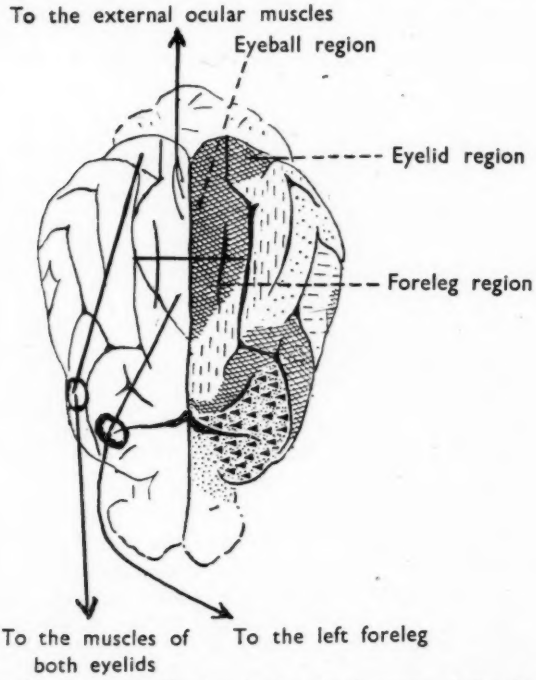

FIG. 4.—Motor localization in the visual cortex of the dog.

of the caudal part, whereas they still occur when the medial-caudal part has been spared, and moreover that these movements can be excited by electrical stimulation of the mesial side of this latter part; (3) that the optic placing reactions and other optic reactions of the forelimb still occur after the extirpation of the whole caudal part, whereas they are abolished or greatly disturbed, the rostral part of the striate areas being amply removed.

Other investigators (Henschen, Gordon Holmes, Brouwer, and others) have brought forward ample evidence that in man and in animals different parts of the retinæ are projected on different parts of the visual cortex. It appears therefore that in the visual cortex of the dog there is not only a motor but also a sensory localization.

It is, however, to be remembered, that in the fore-brains of a dog there is not a separate motor and a separate sensory cortex as in man, but a mixed sensu-motor cortex, and moreover that even in man it is not beyond doubt that the motor cortex (the præcentral gyrus) has exclusively motor functions. Definite optic reactions are usually elicited by optic stimulation in a special part of the visual field, for instance the optic placing reactions by stimulation in the under half of this field. It may be, that by this coincidence a combined motor and sensory localization can be explained. It is another and more likely possibility that these two localizations are located in different layers of the striate area.

The Munk-dog.—Munk has been one of the first to perform the ablation of the caudal poles of the occipital lobes in dogs. According to Munk this extirpation entails "Seelenblindheit" (mind blindness), and impairs temporarily the faculty of recognition.

By the ablation of the caudal poles of the occipital lobes not the whole visual cortex is removed, as Munk supposed, but only the caudal part, whereas the small rostral part is spared (fig. 5, I).

The removal of the caudal part of the striate area entails that the blinking reflexes elicited by threatening movements and also the optic conjugate ocular movements are abolished, and it is due to the absence of these latter movements that the animal makes the impression of being stupid and blind, so that the staff of the laboratory unanimously agrees that it does not see, although it manifests several optic reactions.

The preservation of the rostral part of the striate area brings about that the optic placing reactions still occur. When the animal walks about a room, it can be observed that it does not collide with the wall, but stops at a short distance from it, or goes on in another direction, without touching the wall. When it comes near a low obstacle, then it steps or jumps over it, or goes round it, again without coming in touch with it.[1] On being placed upon a table it walks without hesitation. When

[1]Although these obstacles are promptly evaded, it has, curiously, been observed that the head of the animal came into collision, for instance, with the leg of a table or chair (but not with the wall of the room). It seems, therefore, that the ablation of the caudal part of the visual cortex entails also, at least temporarily, disturbances of the optic reactions of the head.

it comes near the edge of the table it first stops and then goes on in another direction or, if the table is not too high, it jumps from it like a normal animal.

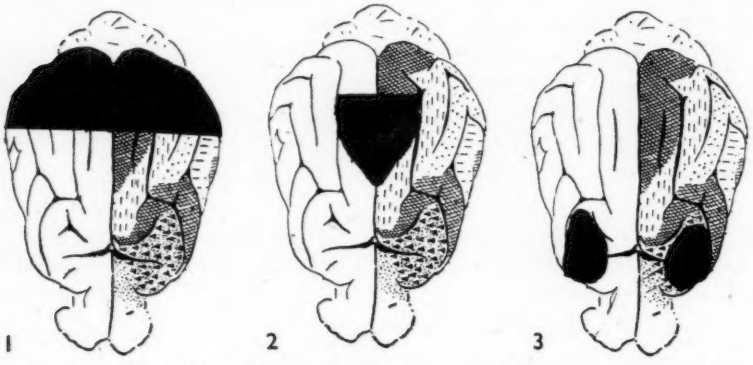

FIG. 5.—I.—Forebrains of the "Munk-dog." II.—Bilateral extirpation of the rostral part of the striate area. III.—Bilateral extirpation of the foreleg region of the motor cortex. The extirpated parts are blacked.

From these observations it is obvious that in the Munk-dog optic impulses can still produce optic reactions of the forelegs (optic placing reactions, walking movements, jumping from a table and over obstacles); and moreover that they can still bring to a standstill and also can modify the motor reactions of these legs. All these faculties are lost after the bilateral extirpation of the whole striate area, it is obvious therefore that they are brought about by the rostral part of this area.

In a dog, wherein the rostral part of both striate areas has been amply removed (fig. 5, II), the blinking reflexes brought about by the sudden appearance of an object near the eyes and the optic conjugate ocular movements still occur, whereas the optic placing reactions are lost.

Although the animal, due to the occurrence of the conjugate ocular movements, makes on everyone the impression that it sees, it bumps against the walls of the room and stumbles over obstacles. If it is placed on a table and is stimulated to walk by pinching its tail, it does not stop near the edge but goes on, and then one of the two following things happens: either one of the forelimbs is placed just on the edge of the table or the edge is passed and the limb slides downwards along the edge.

In the first case the sensory end-organs in the skin of the toes, and in the second case the sensory end-organs in the skin of the dorsal side of

the foreleg are stimulated by the contact with the edge, and the impulses, which thereupon emerge from the stimulated end-organs, and which are conveyed to the central nervous system, bring about that the leg is withdrawn and replaced on the top of the table. It is not by optic, but by sensory impulses that these correcting movements preventing the fall off the table are produced.

The animal never jumps from the table, and every time that it comes near to the edge, one of the two things happens again and again, and it therefore stays, for hours and hours, on the table until it is taken off.

From these observations it is evident that after the bilateral ample removal of the rostral part of the visual cortex optic impulses do no longer elicit optic reactions of the forelegs (no optic placing reactions, no walking movements elicited by optic stimuli, no jumping from the table or over obstacles), and moreover that these impulses can neither stop nor alter the motor reactions of these limbs.

Several months after the extirpation some of these disturbances are less marked and then, for instance, it can often be observed, that the animal on approaching the wall of the room alters his direction and does not come, as before, into collision with it. If the evading of the wall is then brought about by optic reactions (turning) of the head or by a strongly developed tactile sensibility or otherwise could not be established.

A dog wherein the foreleg region of the motor cortex has been amply removed on both sides, thus in other words the whole sigmoid gyrus has been removed bilaterally (fig. 5, III), presents also the optic conjugate ocular movements and the blinking reflexes excited by the unexpected appearance of an object near the eye, whereas the optic placing reactions are again abolished. This animal too bumps against the walls of the room, against chairs and other furniture, and stumbles over low obstacles. If it is placed on a table and urged to walk by pinching its tail, it does not stop at a short distance from the edge, but goes on and falls off the table!

The pathways from the eyes to the striate areas and these areas themselves being uninjured, the anatomical conditions do not exclude the possibility, that the animal sees the edge and the depth round about the table. Nevertheless it falls, whereas in the same circumstances a dog wherein the whole visual cortex has been removed, and which therefore is considered to be blind, does not fall.

By the removal on both sides of the foreleg region of the motor cortex the cerebrospinal pathways to the forelegs are blocked, and therefore neither the optic nor the sensory impulses can bring about correcting

movements of the forelegs, which prevent the fall from the table in normal animals.[1]

It is evident from these observations that the bilateral ample destruction of the foreleg region of the motor cortex entails the abolition of all cerebral reactions of the forelegs brought about by optic and sensory impulses, and furthermore that the motor reactions of these legs are in no way inhibited or altered by optic impulses.

Extreme caution must be exercised in reasoning from experiments on animals to the case of man. In so far, however, as it concerns the blinking reflex brought about by the sudden approach of an object towards the eyes, this is such a primitive and also unconscious reaction that it may be supposed that its central mechanism will be in man almost the same as in animals; a supposition which has been strongly supported by clinical observations.

The optic conjugate ocular movements are equally primitive cerebral reactions, so that it may be presumed again that their central mechanism will be almost the same in man and in animals, and that in man too the optic impulses, which produce these reactions, are conducted from the striate area not via other parts of the cerebral cortex, but along a more direct pathway to the oculomotor nuclei. This is, however, not yet firmly established. With regard to the optic reactions of the forelimbs things are different. These reactions, like most of the other cerebral reactions, are in higher animals, and still more in man, much more influenced by things which have happened before. After every visual observation "something" is left behind in the central nervous system, which may be indicated, in imitation of Semons, as engrams or, by using the terminology of Pavlov, as traces. These "traces" are left behind in some unknown part of the fore-brains, and it is likely that by every successive optic stimulation impulses are conveyed from the striate area to this unknown part of the brains, and that this part responds in its turn by emerging impulses. These impulses can bring about an inhibition of the optic reaction. A typical

[1] In normal animals two kinds of correcting movements can be distinguished: *cerebral* correcting movements elicited by sensory impulses emerging from the sensory end-organs in the skin, and *subcortical* correcting movements excited by impulses from the sensory end-organs in the muscles. The subcortical correcting movements still occur after the extirpation of both cerebral hemispheres and also, of course, after the bilateral extirpation of the foreleg region of the motor cortex. From the above mentioned observation it appears, however, that after this extirpation the subcortical correcting movements of the forelegs are occurring too late and are acting too slowly in order to prevent the fall from the table.

example of this inhibition was observed by the study of the optic placing reactions of the forelimbs in man. If a child of a few weeks old is examined in the same manner as the dogs, no placing reactions of the forelimbs occur. This is presumably due to the fact, that the cerebrospinal pathways are not yet fully developed. In conformity with this supposition the placing reactions occur at the age of 1 year just as automatically as in dogs, but, owing certainly to cerebral inhibition, these reactions are no more notable when the child is 3 or more years old!

These impulses, however, cannot only bring about an inhibition, but they can also replace the inhibited reaction by a modified or quite different reaction. This is the reason that in man the primary optic reactions so rarely occur and that the investigation of their central mechanism is so extremely difficult, and this in its turn is one of the main reasons that it is not known if in man too there is, as in dogs, besides the sensory also a motor localization in the visual cortex.

IV. Optical Nystagmus.

(Optico-kinetic Nystagmus, Train Nystagmus.)

Optic stimuli can produce rhythmic to-and-fro movements of the eyes, called nystagmus, consisting of a rapid motion in one direction (rapid phase) and a less rapid movement in the opposite direction (slow phase). These rhythmic movements of the eyes occur when successive moving objects traverse the field of vision. During the slow phase the eyes move in the same direction as the moving objects so that their images are retained for a while on the same spots of the retina and can therefore be visualized, whereas in immobile eyes the images of moving objects are fused and melted into one another. It has almost universally been agreed: first that optic nystagmus is a *cerebral* reaction, and secondly that for its occurrence it is essential that a *series* of objects move in the field of vision in the same direction.

Some investigators, however, have suggested that only the quick phase is a cerebral reaction, the slow one being subcortical in origin. Most authors, especially clinicians, agree with the view of Bárány that, if a series of objects traverses the field of vision, the eyes follow one object (slow phase) until its successor obtrudes itself into consciousness and that thereupon the fixation reflex comes into play and the second object is fixated (rapid phase), and so on. According to this point of view the rapid phase is a fixating movement, the slow phase a following movement whereby the fixation is maintained.

It is, however, by no means proved, that optic nystagmus is a cerebral

reaction. In man it is an unconscious reaction, whereas most cerebral reactions are conscious. Bartels has observed the occurrence of optic nystagmus in lower animals, by which the fore-brains are not developed or fail altogether. He has therefore put forward the suggestion, that the optic nystagmus is subcortical in origin and is brought about by a primitive mechanism more or less like the tropisms. In clinical examination optic nystagmus is usually excited by moving alternating black and white stripes, thus contrasts, in the field of vision. From the point of view of physics this is such a simple kind of stimulation, that it can hardly be accepted, that it produces exclusively cerebral and not subcortical reactions. Several years ago optic nystagmus in dogs was studied, in collaboration with de Kleyn, by one of us. It was then observed that nystagmus does not occur, as in man, when a black and white striped drum is rotated in the field of vision. The only manner whereby nystagmus could be brought about was to rotate in the visual field a revolving platform, upon which a number of rabbits was placed along the border. But not even then was nystagmus initiated in every dog, but only in those animals which became excited by the rabbits and snapped at them. Nystagmus did not occur if, instead of rabbits, other objects were placed upon the platform.

Thus, the initiation of optic nystagmus in dogs wants a very special and complicated stimulation which excites the instinctive "interest," and thereby it was established that in dogs a cerebral optic nystagmus occurs.

Some time after, however, it was observed in our laboratory by Visser, and at the same time by van der Spek, that in normal and also in *decorticated* pigeons a head-nystagmus is elicited, when they are rotated upon a revolving platform, and that this nystagmus not only occurs at the initiation and cessation, but also during the whole time that the rotation was maintained with an exact uniform angular velocity. The nystagmus occurring during the rotation with uniform velocity cannot be a labyrinthine nystagmus, which is only called into play by acceleration and retardation, and not by uniform movements.

During rotation the whole visual environment rotates in the opposite direction, and it seemed likely that this is the stimulus, which elicits the head-nystagmus occurring during the rotation with uniform velocity. This supposition has been confirmed by the observation, that the head-nystagmus disappears when a cylinder is placed upon the revolving platform round the animal and that it reappears when the cylinder is taken away. Furthermore it was observed that the head-nystagmus also occurs when the pigeon is placed inside a rotating vertical cylinder with alternat-

ing black and white stripes on the inside. It is obvious from these observations, that in pigeons a *subcortical* head-nystagmus occurs.

Thereupon other animals (rabbits, cats, dogs, and monkeys) were examined in the same manner, and then it was observed that in these animals an eye-nystagmus occurs, when they are rotated with a uniform speed, and that this nystagmus too disappears if a cylinder is placed on the revolving platform, and reappears when the cylinder is taken away, and that it also occurs if the animal is placed inside a rotating striped cylinder. Furthermore it was established that in the same circumstances the nystagmus still appears when both cerebral hemispheres have been removed.

It follows from these observations, that in all these different kinds of animals a *subcortical* optic eye-nystagmus occurs, and moreover that in dogs two forms of optic nystagmus can be distinguished: (1) *Subcortical* optic nystagmus, which occurs when all parts of the visual environment are moving in the same direction: (2) *Cerebral* optic nystagmus, which occurs when successive moving objects, which arouse the instinctive "interest," traverse the field of vision.

(1) Subcortical Optic Nystagmus.[1]

This form of nystagmus has been specially studied in rabbits. Photographic records of it were made by means of a beam of light reflected by a small mirror on a moving photo-film; the mirror being attached to a piece of dried shell-membrane from an egg, which was affixed upon the cornea. The piece of shell-membrane covered the whole cornea, so that the eye was blinded and only the other eye could be stimulated by optic stimuli. The head of the rabbit was steadied by the head-fix of Tschermak.

By this investigation it was first of all observed, that in order to initiate the subcortical nystagmus it is not necessary that the whole visual environment is moving; the nystagmus being still produced when a contrastless (black or white) screen is held between the eye and the rotating striped cylinder. This holds good if the screen occupies the central part of the field of vision, so that only the periphery of the retina is stimulated by the rotating cylinder, and also when it occupies a peripheral part of the visual field. This demonstrates that the motion of images on a part of the retina is already sufficient. *In the dark, nystagmus is even brought about by the movement of one single lightpoint (small electric lamp) in the field of vision!* (fig. 6).

[1] For further details concerning the mechanism of the optico-kinetic nystagmus *see*: J. W. G. Ter Braak, *Archives Néerlandaises de Physiologie de l'homme et des animaux*, 1936, **21**, 309.

It results from these observations that the generally accepted view that the initiation of optic nystagmus necessitates the movement of a *series* of objects can no longer be maintained. Furthermore it follows that the rapid phase is not a fixation-movement, whereby the next object is fixated; the rapid as well as the slow phase being produced, under special conditions, by the movement of one single object.

Only in the dark is optic nystagmus elicited by the movement of a single electric lamp. In the light it is the immobile objects in the field of vision which prevent its occurrence.

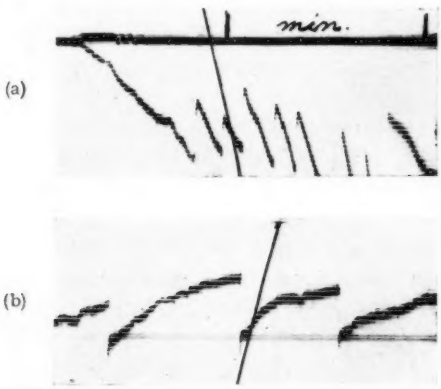

FIG. 6.—Nystagmus brought about by the movement in the dark of a small electric lamp with an angular velocity 51′/sec.: (*a*) the lamp traverses the field of vision in oral direction, (*b*) movement of the lamp in caudal direction; the nystagmus in opposite direction produced by this movement is less frequent.

If an object moves in the field of vision to the right, then its retinal image moves to the left, and it is evident that it is due to the latter movement that the eyes follow the moving object. A movement of the retinal image to the *left* excites a movement of the eyes to the *right*.

But, as soon as the eyes follow, the movement of the retinal image of the moving object becomes less or stops altogether, and at the same time the retinal images of immobile objects are moving in the opposite direction! By this movement in the opposite direction, thus to the right, a deviation of the eyes to the left will be produced with the result, that the primary following movement, as soon as it starts, is checked and neutralized, so that this movement and therefore also the nystagmus does not occur.

That it is really the image of immobile objects which prevent the occurrence of optical nystagmus was confirmed by the following experiment.

In a rabbit one of the eyes was immobilized by an apparatus specially made for this purpose and this eye was stimulated by moving objects while the movements of the other, covered, eye were recorded in the described manner.

In these circumstances, whereby movements of the retinal images of immobile objects are prevented, nystagmus of the recorded eye was excited, not only in the dark but also in bright light, by the movement of a single object in the field of vision of the immobilized eye.

A real black field does not stimulate the retina. It is well stimulated by an equal white field, but this is not the stimulation which brings about the impulses producing optical nystagmus. If an animal is placed inside a rotating black or entirely white cylinder no nystagmus is produced, whereas it occurs when one-half of the cylinder is black and the other half white. But it is not by the black and white fields, that the nystagmus is then initiated, but by the transitions from the one into the other.

It may be asked if both transitions, from white into black and from black into white, are effective. When the white half of the cylinder comes into and progresses in the field of vision more and more successive parts of the retina are stimulated, and more and more sensory end-organs are brought into the excitatory state, by which the impulses are promoted which are conveyed to the central nervous system. The white half produces a progressive excitatory process. If thereupon the black half comes into and traverses the field of vision the excitatory state of more and more successive sensory end-organs is extinguished.

The experiment with the half-white, half-black cylinder has shown that only the appearance and progress of the white, and not of the black half, in the field of vision gives rise to optic nystagmus. And also by other investigations it was demonstrated that the progress upon the retina of an increase of excitation (produced by greater luminosity) elicits nystagmus, whereas a progressing decrease of excitation (by smaller luminosity) has not this effect.

The gradual progression upon the retina of greater luminosity provides the stimulus, which brings about the subcortical optic nystagmus, and it is the direction of the progression which determines its direction.

It has not been studied if subcortical nystagmus can be produced also by moving transitions from one colour into another of equal luminosity.

It is a remarkable feature that in rabbits, with their laterally directed eyes,

optic nystagmus is better produced by a movement of contrasts in forward (nasal) direction than by the movement in the opposite (caudal) direction.

After the ablation of both cerebral hemispheres optical nystagmus still occurs with typical slow and rapid phases. It is therefore ascertained that not only the slow, but also the quick phase is subcortical in origin.

If the nystagmus is excited by a rotating striped cylinder it usually begins with a slow phase. It is, however, possible to produce a nystagmus which starts with a rapid phase, viz. under the following conditions. When the stimulation by the cylinder is suddenly interrupted by switching off the light the nystagmus is first maintained (optic after-nystagmus), then the eyes deviate slowly in the direction of the slow phase, and thereupon this deviation is maintained for a short time, after which the eyes return slowly into the primary position. If, by switching on the light, the stimulation is started again at a moment when the eyes are still deviated, then the nystagmus reappears and it begins not with a slow, but with a rapid, phase. It results from this observation that not only the slow, but also the quick phase is brought about by optic, and not by proprioceptive impulses emerging from the ocular muscles.[1]

It seems that the optic impulses activate a rhythmically acting centre ("nystagmus-centre") which brings about alternately slow contractions of the ocular muscles which deviate the eyes in one direction, and rapid contractions of the ocular muscles which rotate the eyeballs in the opposite direction.

The movement of the retinal image provides the stimulation, which causes that the eyes follow the moving object and rotate in the same direction. This stimulation, however, becomes less as soon as the eyes follow, and ceases when the eyes are rotating with the same angular velocity as the moving object. The image is then retained on the same spots of the retina, so that its influence is lost. It may therefore be expected that the angular velocity of the slow phase will always be less than that of the moving object.

In reality, however, the angular velocity of the slow phase and of the moving objects is almost always equal!

As is shown by the records, the eyeballs rotate during the slow phases

[1] The same holds good for the labyrinthine nystagmus, both its phases are subcortical in origin, and moreover it has been observed by de Kleyn, that the rhythmic contractions of the ocular muscles, producing this nystagmus, still persist when the eyeball has been eviscerated, and the proprioceptive nerve-endings in the muscles have been thrown out of action by cocaine.

with almost the same angular velocity as the rotating striped cylinder, by which these phases are produced.

In order to investigate the mechanism, by which this is accomplished, one eye of a rabbit was again immobilized, and the movements of the other, covered, eye recorded. The striped cylinder was rotated around the animal with an exactly uniform speed. Under these circumstances the retinal images are moving in the immobilized eye all the time with the same angular velocity as the rotating contrasts, and their velocity is not altered any more by following or other movements of the eye.

It was observed by this investigation, that the displacement of images with uniform speed upon the retina of the immobilized eye excites nystagmus of the recorded eye with slow phases, in which the eye rotates with an angular velocity many times greater than those of the moving contrasts, traversing the field of vision of the immobilized eye. A rotation of the striped cylinder with an angular velocity of 1/6°/sec. produced slow phases with an angular velocity of 2·7°/sec., thus with a 16 times greater speed!

In a non-immobilized eye the displacement of the retinal images of moving contrasts will initiate also slow phases with an angular velocity, which is greater than the velocity of these contrasts. However, as soon as the velocity has become greater, the retinal images do not move more in the primary, but in the opposite direction and this entails that the velocity will be diminished. If thereby the speed of the eye-rotation has become less than the velocity of the moving contrasts, the images move again in the primary direction, with the result, that the velocity of the eye-rotation will increase, and so on.

In this way a regulation is reached, which ensures that the angular velocity of the eye-rotation of the slow phase does not become much greater nor much less than the velocity of the contrasts traversing the field of vision. It ensures thus that the velocity of the moving contrasts and that of the rotation of the eye-balls, produced by them, are always almost equal.

By this regulation the images of moving objects are retained on the same spots of the retina, so that visual appreciation is allowed, and the physiological purpose of the slow phase is fulfilled. It brings about a regional fixation, not, however, the fixation which is usually designated by this name, and whereby the image of an object is brought and maintained on the fovea centralis, but a fixation by which the images of a moving visual environment are retained on the same spots of the retina.

A rotation of the cylinder with a high speed does not produce nystagmus, presumably by the fusing of the retinal images of the moving contrasts. If the speed is gradually diminished, then it can be noted that at a certain speed nystagmus occurs, but at this maximal speed the eyes still cannot follow the contrasts with equal velocity. The maximal angular velocity whereby nystagmus occurs amounts in most rabbits to 20 to 40°/sec., in some rabbits to 70°/sec., in dogs and monkeys to more than 360°/sec.

By diminishing the angular velocity of the cylinder more and more, it was observed that in rabbits nystagmus is still produced by very slow rotations, even by a rotation of 6·4″/sec., thus by a rotation of the cylinder of 360° in 2½ days.

The nystagmus is then brought about by a movement which cannot be visually appreciated in man. According to Aubert, Bourdon and others the angular velocity of 1/10′/sec. is the smallest, by which movement can still be visually appreciated.

During the slow phases of this nystagmus the deviation of the eyes progresses very slowly during more than fifteen minutes, and it is not until then that it is interrupted by a quick phase. The angular velocity is thereby again almost equal to the velocity of the cylinder, so that the deviation, which is reached in the fifteen minutes, amounts to almost $15 \times 60 \times 6{\cdot}4' = 1{\cdot}6°$.

The contraction of the ocular muscles, by which this slow phase is brought about, progresses so slowly, that it must be accepted that the motor units are thrown into action almost one by one, and not several together.

A slow rotation of the contrasts produces slow phases with small angular velocity and of long duration, thus a nystagmus of low frequency, whereas a more rapid rotation of the contrasts produces slow phases with greater angular velocity and of shorter duration, thus a nystagmus of higher frequency.

If the angular velocity of the rotating cylinder, and therefore also of the slow phases, is increased, the average amplitude of these phases usually becomes greater. This increase of the amplitude occurs, although the duration of the slow phases diminishes, and it is evident, therefore, that the increase of their angular velocity is usually greater than the decrease of their duration. The amplitude, and therefore also the duration, of the slow phases varies in different animals, and in some rabbits the average amplitude is constantly smaller than in others. But even in the same rabbit and under the same conditions, for instance during a rotation of

the cylinder with a uniform angular velocity, the amplitude of the succeeding slow phases is, due to unverified causes, not always the same.

If the stimulation by the rotating cylinder is abruptly checked by switching off the light, the optic nystagmus does not disappear at once, but continues for some time (*optic after-nystagmus,* fig. 7).

Optic after-nystagmus has been observed in pigeons (of the head), rabbits, cats, dogs, and monkeys. In these last animals it is particularly marked, and optic after-nystagmus of 40 and more jerks has been noted.

FIG. 7.—Optic after-nystagmus. At the black vertical line cessation of the stimulation.

It seems that the activity of the central mechanism does not come at once to an end by cessation of the stimulation, but that an internal inertia comes into play and after-discharge occurs. If the nystagmus is initiated by a movement of contrasts with uniform speed (by switching on the light inside the cylinder), then the first slow phases have not immediately the same angular velocity as the moving contrasts, but this velocity is gradually reached. It seems therefore that at the initiation an internal resistance in the central mechanism has to be overcome.

The optic nystagmus and the optic after-nystagmus have the same direction, whereas the direction of the labyrinthine nystagmus and the labyrinthine after-nystagmus are opposite. One may be inclined to consider this as an essential difference, from which it may be concluded, that the optic and the labyrinthine nystagmus are brought about by different central mechanisms.

The optic after-nystagmus, however, is due to after-discharge, whereas the labyrinthine after-nystagmus is owing to the inertia of the labyrinthine fluid which tends to persist in its movement after the abrupt cessation of a rotation. The labyrinthine after-nystagmus is not produced by after-discharge, but by a reversed stimulation, and therefore it is better indicated by stop-nystagmus than by after-nystagmus.

If an animal is rotated upon a revolving platform both labyrinthine

and optic nystagmus are excited; the former by the rotation of the labyrinths, the latter by the movement of the visual environment in the opposite direction. In order to elicit a pure labyrinthine nystagmus free from the influence of vision, the eyes must be kept shut, or a cylinder must be placed on the platform so that the visual field is rotated with the animal. If these conditions are fulfilled, and the animal is rotated with a uniform speed, then nystagmus occurs only at the initiation and after the cessation of the rotation, and not in the interval between. But the nystagmus which occurs at the initiation persists longer than the current of the labyrinthine fluid, by which it is elicited, and also after the cessation of the rotation the nystagmus is maintained longer than the current of the labyrinthine fluid in the reversed direction. In rabbits an accelerated and also a retardated rotation during less than one second excites a nystagmus, which lasts for more than half a minute. Thus in both circumstances, at the initiation and at the retardation and cessation of the rotation, the effect of after-discharge can be observed.[1] It is obvious therefore that the difference in direction of the optic after-nystagmus, and the labyrinthine nystagmus occurring after the cessation of a rotation, does not provide arguments against the view that the optic and labyrinthine nystagmus are brought about by the same central mechanism.

Evidently in labyrinthine nystagmus the four following phases may be distinguished: labyrinthine nystagmus produced by acceleration, labyrinthine after-nystagmus due to after discharge, labyrinthine stop-nystagmus produced by the retardation and cessation of the rotation, and labyrinthine after-stop-nystagmus owing to after discharge after the cessation. According to Bárány, and to Fischer and Wodak a prolonged rotation is followed after the cessation, first by a nystagmus in the opposite direction, and then by a nystagmus, in the same direction as the primary nystagmus produced by the initiating of the rotation. This nystagmus may be designated as after-after-stop-nystagmus.

The slow phase of the labyrinthine nystagmus, as well as the slow phase of the optic nystagmus, does not reach immediately, but gradually the same angular velocity as the rotating movement, by which it is produced. Moreover the records of the optic and of the labyrinthine nystagmus show the same characteristics, and their records cannot be

[1] Steinhausen has studied the labyrinthine reactions of spikes, and from his observations he concludes, that the maintenance (long lasting) of the nystagmus after the cessation of the stimulation is not due to central after-discharge but is owing to the small elasticity of the cupula, by which it is brought about that the deviated cupula returns very slowly to its initial position. It has, however, been observed by Mowrer, who registered in chrysemys picta the action currents of the vestibular nerve occurring during the acceleration and retardation of a rotation, that these currents almost immediately disappear, when the angular velocity has become uniform.

distinguished from each other. These facts support the suggestion that both forms of nystagmus are brought about by the same central mechanism.

The fact that the records cannot be distinguished applies only to nystagmus of an average frequency; a nystagmus of low frequency being produced in rabbits only by optic stimuli, whereas a nystagmus of high frequency can only be brought about by labyrinthine stimulation.

If dogs are kept in dim illustration for six or seven weeks a pendular nystagmus with frequent small jerks develops. It has been observed by de Kleyn that by rotating these dogs on a revolving platform two kinds of nystagmus occur simultaneously at the initiation and after the cessation of the rotation. Also in the records the two kinds of nystagmus, the one superimposed on the other, and each with its own frequency and amplitude, can be distinguished. It is evident therefore that they are brought about by two different central mechanisms, which are acting quite independently of each other.

If an animal is rotated, with open eyes, upon the revolving platform then the visual environment moves during the whole rotation in the opposite direction and therefore optic nystagmus will be excited. But at the initiation and at the retardation of the rotation the labyrinthine stimulation comes also into play and labyrinthine nystagmus will be produced. It may therefore be expected that in these circumstances again two kinds of nystagmus will occur, but in fact only one nystagmus can be observed, and also in the records only one nystagmus, brought about by summation, can be noted.

At the initiation of the rotation the combined stimulation brings about that the slow phases reach sooner the same angular velocity as those of the revolving platform or, in other words, of the rotating visual environment. The combined stimulation, of course, cannot achieve a rotation of the eyes with a angular velocity which is greater than those of the visual environment, because this would give rise to a movement of the retinal images in the opposite direction with the result that the movement would be immediately checked and the velocity diminished.

When the angular velocity of the rotating platform has become uniform the labyrinthine stimulation ceases, and a pure optic nystagmus, brought about by the rotating environment, occurs.

After the cessation of the rotation, the optic stimuli will produce, by after-discharge, an after-nystagmus in the same direction, whereas the reversed labyrinthine stimulation will excite a stop-nystagmus in the opposite direction, with the result that no nystagmus occurs! The optic after-nystagmus and the labyrinthine stop-nystagmus are neutralizing each

other. Whereas, in man as well as in animals, a labyrinthine stop-nystagmus can be observed after the cessation of a rotation with shut eyes, no nystagmus occurs after a rotation with open eyes.

Rotation to the right	*Labyrinthine stimulation*	*Optic stimulation*	*Combined stimulation*
At the initiation	Nystagmus to the right	Nystagmus to the right	Nystagmus to the right
Uniform velocity	(No nystagmus)	Nystagmus to the right	Nystagmus to the right
After the cessation	Stop-nystagmus to the left	After - nystagmus to the right	(No nystagmus)

The labyrinthine stimulation is more effective than the optic, but usually of short duration. The labyrinthine stimulation, therefore, is especially adapted to initiate the nystagmus, whereas the optic stimulation is particularly suited for its maintenance.

The greater effectiveness of the labyrinthine stimulation is especially evident by comparing the acceleration of the slow phases. The maximal acceleration, which has been noted of the slow phases elicited by optic stimulation, amounted to 10'sec.^{2}, but this acceleration was reached only when the stimulated eye was immobilized, while the movements of the other, covered eye were registered, whereas an acceleration of 120° /sec.^{2} (more than 700 times greater!) of the slow phases, produced by labyrinthine stimulation, was frequently observed.

It is evident, therefore, that the slow phases reach much quicker by labyrinthine than by optic stimulation the same angular velocity as those of the rotation, by which the nystagmus is excited. A very rapid rotation of the animal is always followed by nystagmus even if the eyes were open during the rotation. This is due to the fact, that by a rapid movement of the visual environment the retinal images are fused and do not excite either primary or after nystagmus, so that the labyrinthine stop-nystagmus is not neutralized. In order to study the effect of the combined stimulation a number of other experiments were carried out, by which first a uniform optic stimulation, producing a nystagmus to the right or to the left, and thereafter a labyrinthine stimulation, producing a nystagmus in the same or opposite direction, was thrown into action. The same experiments were also performed on rabbits, whereby one of the eyes was immobilized and the movements of the other covered eye were recorded. In these circumstances a successive labyrinthine stimulation, producing a nystagmus in the same direction as the optic nystagmus.

brings about an increase of the angular velocity and of the frequency of the slow phases, whereas a successive labyrinthine stimulation, exciting nystagmus in the opposite direction, entails either a decrease of the angular velocity and frequency of the slow phases or, the labyrinthine stimulation being stronger, a neutralization of the foregoing optic nystagmus, while, if a still stronger labyrinthine stimulation is applied, a nystagmus in the reversed direction occurs.

It appears from all these observations that the result of the combined optic and labyrinthine stimulation is always a, almost algebraic, summation of their influences. This supports strongly the view, that the subcortical optic and the labyrinthine nystagmus are brought about by the same central mechanism, by the same "nystagmus-centre."

Bárány has put forward the view that only the slow phases of the labyrinthine nystagmus is peripheral in origin and elicited by the impulses emerging from the labyrinths, whereas he considered that the rapid phase is of central origin, depending on the supra-nuclear gazing centre ("Blick-centrum") in the pons.

It appears from our observations, that both phases are produced by a subcortical rhythmically acting centre (nystagmus-centre), which can be activated by optic and by labyrinthine impulses. It seems probable that this nystagmus-centre is identical with or related to the pontine gazing centre, but the exactness of this view is not at all proved.

The subcortical optic nystagmus still occurs, also in monkeys, after the removal of both cerebral hemispheres. This does not mean, that the fore-brains have no influence at all on this reaction. If the optic nystagmus was initiated by gradually diminishing the angular velocity of the rapidly rotating cylinder, it has been noted that in normal dogs nystagmus occurred, when the velocity was lowered to ± 400°/sec., whereas after the ablation of the cerebral hemispheres, and also after the bilateral removal of the striate area, nystagmus did not appear until the velocity has been lowered far more. After the unilateral extirpation, for instance of the right cerebral hemisphere, the optic nystagmus to the right was still excited by an angular velocity of 400°/sec., whereas the nystagmus to the left did not occur until the velocity had become much less. This asymmetry remains.

In rabbits a similar asymmetry has been observed, but only in the first week after the unilateral ablation. It is interesting that in monkeys this asymmetry does not occur, and moreover that after the removal of both cerebral hemispheres optic nystagmus can still be elicited by contrasts traversing the field of vision with high angular velocity.

(2) Cerebral Optic Nystagmus.

Whereas in order to initiate the subcortical optic nystagmus it is essential that the moving objects or contrasts occupy the greatest part of the visual field, the occurrence of the cerebral optic nystagmus necessitates the traversing of the field of vision by objects which arouse the instinctive or psychic interest. The attempts to excite cerebral optic nystagmus in rabbits have all failed.

In dogs, as has been mentioned above, cerebral optic nystagmus can be elicited by rotating in the field of vision a revolving platform, whereupon a series of rabbits has been placed; but only in dogs in which the instinctive sporting interest is aroused by the rabbits. This cerebral nystagmus is abolished after the removal of the cerebral hemispheres and also after the extirpation of the striate areas, but it still occurs after the bilateral ablation of the motor cortex. From this observation, which has been confirmed by de Kleyn and Broers, results that the optic impulses, which bring about the cerebral optic nystagmus, do not pass from the striate area through the motor cortex, but are conveyed along another path (via the superior colloculi?) to the nuclei of the oculomotor nerves. After the ablation of one hemisphere the cerebral optic nystagmus is asymmetric; the right hemisphere being removed the nystagmus to the right still occurs whereas the nystagmus to the left (to the hemianopic side) has disappeared. This asymmetry persists during the further life of the animal.

In monkeys (macacus rhesus) the cerebral optic nystagmus can be easily excited, for instance by a human subject traversing slowly its field of vision, the head of the animal being fixed by a hand.

A nystagmus of 3-4 jerks then occurs.

This nystagmus is abolished after the removal of both cerebral hemispheres, and also after the bilateral extirpation of the striate area. After the ablation of one cerebral hemisphere a similar asymmetry as in dogs has been observed, but this asymmetry had already disappeared a month after the injury, while after the unilateral destruction of the striate area even the first day after the operation cerebral optic nystagmus in both directions could be elicited.

These observations demonstrate a striking difference between monkeys and dogs, wherein the ablation of one hemisphere and also the unilateral removal of striate area entails a permanent asymmetry.

In man cerebral optic nystagmus can be excited by moving slowly a string of alternating black and white or coloured wooden beads, or a series of small coloured prints at some distance from the eyes. The beads

occupying only a small part of the field of vision, the nystagmus produced by them is certainly cerebral in origin.

Nystagmus is only excited, if the subject looks with attention at the beads. In older children and in adults this can be obtained by giving the order to look at them. By each slow phase one of the beads is then followed with the eyes. One may, therefore, be inclined to give the order to follow the beads with the eyes, but this is wrong. If this order is given and it is obeyed, then the eyes follow as far as possible, namely till the fixated bead has reached the limit of the practical field of fixation, and no nystagmus occurs. Therefore, if the beads are followed voluntarily with the eyes, this must be forbidden.

By each slow phase of the nystagmus a bead is followed only for a certain distance, and then this movement is interrupted by a rapid phase. It is evident therefore, that the slow phase is not a voluntary, but a reflex following movement.

If the subject looks with attention at the moving string, then one of the beads is fixated and its image brought upon the fovea centralis, which is maintained for some time by the slow phase, so that it can be seen distinctly. At a certain moment the involuntary reflex movement of the slow phase is interrupted and followed by a sharp jerky movement in the opposite direction. It is accepted by most authors that this rapid phase occurs when a successional object attracts the attention and therefore is fixated. According to this view the rapid phase must be considered as a fixation-movement. This view, however, is not exact, the quick phase occurring also if the subject looks with attention at a single moving object without following it voluntarily with the eyes. Furthermore, Stenvers and also Ohm have pointed out, that in cases of tractus-hemianopia optic nystagmus in both directions still occurs, and that thereby it can be noted that the rapid phase is initiated before the next successive object has reached the intact part of the field of vision. If, after the rapid phase, a successional object attracts the attention the next slow phase occurs, by which the image of the successional object is first brought upon, and thereon retained for some time on the fovea centralis. The slow phase of the cerebral optic nystagmus may therefore be considered as a series of fixation-movements.

It has been observed by Dodge and others, that the act of fixating an immobile object is likewise brought about by a constant activity of the ocular muscles, which results in two kinds of fine rotatory movements of the eyes, which although they may seem at rest, are never completely immobile.

The slow phases of the subcortical as those of the cerebral optic nystagmus, are fixating movements, whereas the rapid phases of both kinds of

nystagmus are only movements, by which the slow phases are rhythmically interrupted, owing to the rhythmical activity of the central mechanism.

By the fixation-movements (slow phases) of the subcortical optic nystagmus all the images of the moving visual environment are maintained on the same spots of the retina, whereas by the fixation-movements (slow phases) of the cerebral optic nystagmus the image of one moving object is brought and retained upon the fovea centralis. The rhythmical activity of the central mechanism of the subcortical optic nystagmus is thrown into action by the optico-physical conditions in the field of vision, notably when moving contrasts traversing the field of vision in the same direction occupy a greater part of this field than the immobile contrasts, whereas the rhythmical activity of the central mechanism of the cerebral optic nystagmus is activated by the movement in the visual field of dominant objects, that is to say, of objects which dominate because they attract the psychic or instinctive attention.

Whether by both influences the same or different rhythmically acting mechanisms are thrown into action, in other words, whether the subcortical and cerebral optic nystagmus are brought about by the same or by different nystagmus centres, is not yet established.

According to Stenvers the optic impulses, eliciting optic nystagmus in man, are conveyed from the striate area to that part of the frontal lobe, which produces a deviation of the eyes to the opposite side, when electrically stimulated. This view is based on the observation of asymmetric optic nystagmus in cases with lesions (tumours, cysts, abscesses) in the temporal, parietal or frontal lobes. In these cases the nystagmus to the side of the lesion occurred normally, whereas the nystagmus to the other side was, often only temporarily, either abolished or less marked and irregular. Also Holmes and Fox have put forward the view, that for the occurrence of cerebral optic nystagmus the integrity of certain regions of the fore-brain is necessary, especially the lower parts of the parietal and frontal lobes.

Extreme caution, however, must be exercised in drawing conclusions from the disturbances, due to tumours, abscesses, etc., with regard to the physiology of the central nervous system, still more if the disturbances are produced by unilateral lesions. A permanent total disappearance of cerebral optic nystagmus caused by a bilateral lesion of the frontal lobes has never been observed. It is therefore not established that in man the impulses, eliciting the cerebral optic nystagmus, are conducted via the frontal lobe, and not, as in dogs, along a more direct pathway to the oculomotor nuclei.

In a patient from the ophthalmic clinic at Leiden, in whom, some years before, the occipital lobe on one side was removed, it has been noted that after this removal cerebral optic nystagmus in both directions still occurred. It appears from this observation that in man, as in monkeys, the unilateral ablation of the visual cortex does not entail, as in dogs, a persisting but only a temporary asymmetry.

It will be asked if in man, as in dogs, two forms of optic nystagmus can be distinguished. From the above mentioned observations it is evident that cerebral optic nystagmus occurs; the nystagmus excited by a string of beads being certainly cerebral in origin. In man, too, nystagmus occurs if the subject is placed inside a rotating striped cylinder, even when it wears Frentzen's spectacles, so that the black and white stripes can hardly be seen. But even then it is not certain that no attention is payed to the stripes, so that it is not beyond doubt that the occurring nystagmus is really subcortical, and not cerebral in origin. We did not have the opportunity of studying optic nystagmus in cases of anencephaly, but in cases of extreme idiocy it was observed that nystagmus occurred, when the subjects were examined inside the rotating striped cylinder, whereas it was not excited by the to-and-fro movement of a string of beads or a series of coloured prints at some distance from the eyes. It seems therefore that in man too subcortical optic nystagmus occurs. If this is confirmed, then it may be presumed that the central mechanism of this primitive, and also unconscious subcortical reaction will be almost the same in man as in animals.

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ELECTROENCEPHALOGRAPHY WITH PHARYNGEAL ELECTRODES.

BY

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Introduction.

Records of the electrical activity of the brain have been made from a "basal" electrode by several workers in North America. Such electrodes are inserted through the nasal passage and rest against, or are imbedded in, the mucous membrane of the roof of the nasopharynx. Originally it was believed that the activity recorded by this method originated in the diencephalon. Grinker and Serota (1938) first used a sharply pointed wire electrode, insulated except at the tip and imbedded into periosteum of the sphenoid bone. Potential differences were recorded between this point and a "diffuse" lead attached to the ear lobe. They claimed that the rhythm thus recorded was slower than that recorded from the scalp over the vault and, from "increased excitation" seen in this basal electrogram during faradic stimulation of the pharynx and also during an attempt to arouse strong emotions in patients, they concluded that it represented the electrical activity of the hypothalamus. Both Grinker (1938) and Hoagland (1938) described slow waves appearing first in basal or pharyngeal leads during states of emotion. In 1942 Grinker reported that cold, epinephrine and electrical stimulation increased this basal rhythm in normals, but not in schizophrenics, and assumed that the cortical pattern is more variable in the latter than that obtained from the basal lead! However, Hoagland, Cameron, Rubin and Tegelberg (1938) observed that the basal electrode provides a very diffuse lead to many diencephalic and mid-brain structures so that it is difficult to attribute potentials obtained from it to any particular area, especially to such a small area as the hypothalamus.

They stressed that the alpha rhythm in both the basal and cortical leads was abolished by opening the eyes indicating a similar origin in the visual system, and that undetected facial movement may produce disturbing artefacts in the pharyngeal lead which are difficult to interpret.

Jasper (1941), using a different technique from that of Grinker, examined epileptics. Grinker, using unipolar electrodes, compared the activity at the basal electrode with that at other electrodes placed on the scalp. The common reference point, or "earth," was connected to the ear. In the bipolar technique all electrodes are "active" and the records

show potential changes between the basal electrode and others placed on the scalp. The phase-reversal method developed by Adrian, *et al.* (1934), was used to locate the origin of the potentials. By this method Jasper showed that in some epileptic prodromes and equivalents the abnormal slow waves appeared only at the basal electrode and not at those placed on the scalp. During an exploratory craniotomy on a boy with *petit mal*, electrodes were placed in line along the base of the hypothalamus and left in place for twenty-four hours. From these electrodes Jasper recorded during subsequent *petit mal* attacks. He showed that the 3 c./sec. waves appeared first from the mid-hypothalamic lead before spreading to involve the cortex. This was considered direct evidence of the diencephalic origin of *petit mal* attacks.

Further evidence in favour of a basal origin for *petit mal* comes from two sources. First, Hursch (1945) examined two epileptic patients after almost complete transection of the corpus callosum. In both cases, bilateral symmetrical spike and wave discharges continued to occur on the two hemispheres. Since the principal intercortical conduction pathways had been cut, the existence of a cortical focus with spread could be excluded. It was suggested that the thalamus or hypothalamus was the probable pacemaker for the discharge.

The second reason for considering that the *petit mal* attack has a basal origin is derived on theoretical grounds. The spike and wave discharge is normally a symmetrical bilaterally synchronised rhythm. It is generally believed that such rhythms are concerned with basal functions. Thus Walter and Dovey (1944) and Cobb (1944) have shown that the abnormal rhythms seen in tumour in the region of the 3rd ventricle have these characters. Kennard (1942, 1943, 1944), in experiments on monkeys and chimpanzees, showed that chronic lesions of the subcortical nuclei produce general changes in the EEG, although lesions restricted to cortical tissue caused no such changes. Epilepsy, or spike and wave discharges in the EEG were frequent findings following lesions to basal ganglia. Lesions of the hypothalamus caused great slowing of the cortical rhythms and diminution of their amplitude. Partial ablation of thalamus or hypothalamus temporarily alters cortical EEGs, but only when both thalamus and hypothalamus are completely extirpated are these cortical potentials abolished. Obrador (1943), in experiments on cats, also showed that lesions of the thalamus or thalamocortical pathways abolish the cortical EEG.

Since the early experiments of Grinker, Hoagland and Jasper, criticism of the basal electrode technique has appeared. This has been reviewed

by Masserman (1943). It is generally accepted that such an electrode is a very diffuse lead and that there is no reason for supposing that the rhythm recorded comes specifically from the hypothalamus. For this reason, it is no longer believed that the activities of this area in normal and abnormal psychological states can be studied by this technique. Hoagland, *et al.* (1938), considered that externally placed electrodes, either for recording from or stimulating the brain, do not provide a valid method for the study of the functions of specific areas. The significance of Jasper's findings in the case of *petit mal*, supported as they are by quite different experimental work, remains, however, undetermined.

Method.

Recording was made with a three-channel Grass standard electroencephalographic equipment. At first, a single pharyngeal electrode was used, and later two electrodes were implanted, one through each nasal passage. It was found unnecessary to use the "spike" electrode (Grinker) after the initial experiments.

Pharyngeal electrode.—A piece of wire 16 cm. long was insulated with shellac throughout its length. The distal end was silver plated by the electrolytic method to form an expansion with a flattened face. This was subsequently chlorided. The proximal end was passed through a rubber cork to which elastic bands were attached. By these bands the electrode, after insertion, could be held by adhesive tape to the cheeks. Provided the tension in the rubber bands was adequate and the electrode properly placed, little movement between the face of the electrode and the mucous membrane occurred.

Preparation of nasopharynx.—The nasal passages were first sprayed with 3 per cent cocaine solution, then cocaine paste[1] was inserted by means of a probe through the length of the inferior meatus as far as the roof and posterior wall of the nasopharynx. The electrode was not inserted until the probe could be freely moved without discomfort as far as the pharyngeal walls. Despite care and practice in the technique there is no doubt that considerable variability of electrode placement results in different cases. This variability was confirmed by radiography after implantation of the electrodes on a few occasions.

[1]Cocaine hydr.	... ...	120 grains
Desiccat. adren. gland	... ...	24 grains
Chloretone	... ...	1 grain
Paraff. liquid	... ...	220 minims
Vaselin. alb.	... ... ad	1 oz.

Electrode arrangements.—Records were made in the following ways:—

(1) Using a single pharyngeal electrode as one of a triangle (Jasper), the electrode being common to two channels connected in series. The scalp electrodes were placed either on frontal and vertical areas, i.e. antero-posterior, or on each temporal area, i.e. transverse.

(2) Using two pharyngeal electrodes, one passed through each nasal passage, records were obtained, (*a*) independently from these and also from paired scalp electrodes; (*b*) using the pharyngeal electrodes as the middle pair of four, the other two being on the scalp. With this technique not every experiment was successful because of artefacts due to breathing, facial movements or too high or too low inter-electrode resistance.

Results.

Twelve patients have been examined with the pharyngeal leads; three on more than one occasion. Three of these patients were epileptics, two had pituitary tumours, four were psychiatric patients and three were normal subjects.

Examination of normal subjects (Records I—III), both with single and double (independent) pharyngeal electrodes, showed that little alpha rhythm activity is recorded by this route. When the eyes of a normal subject were exposed to a flickering light at 7 c./sec. (Record II) the cells of the visual cortex showed a regular rhythm of this frequency, but no such activity could be seen in the record obtained between the pharyngeal lead and the frontal cortex. This suggests that the activity recorded from the pharyngeal lead is not produced by cells involved in alpha rhythm production. In the majority of records obtained from pharyngeal leads, both single and double from normal subjects, low voltage activity of beta frequency could be seen (Records I, II, III). Whereas opening of the eyes (Record III) produced blocking of rhythm of alpha frequency from scalp leads, no change was apparent in the record from paired pharyngeal electrodes.

Using a single pharyngeal electrode, bursts of spike and wave complexes were recorded from an epileptic subject. With bipolar leads arranged in a triangle (Record IV), phase reversal for both spikes and waves could be repeatedly obtained at the pharyngeal electrode. When two pharyngeal electrodes were implanted in the same subject complex groupings of waves and spikes of low voltage were obtained from these electrodes at the time when typical wave and spike discharges were seen from the scalp leads (Record V *a* and *b*). In Record V*a* and VI*b* the discharge is seen first in the frontal scalp leads and after delay of nearly half a second appears in the record of the pharyngeal leads. On the other

hand, in Records V*b* and VI*c*, taken a little later from the same subject, the wave and spike discharge appeared at approximately the same moment from scalp and pharyngeal leads, although the delta activity preceding the outburst appeared first in the scalp leads. On other occasions irregular slow delta activity appeared first in the frontal scalp lead, then in the pharyngeal lead, and persisted in the latter after the discharge had disappeared in the record from the frontal scalp leads (Record VI*a*). While the wave and spike discharge in this subject appeared on occasions first in the frontal scalp leads, and on other occasions simultaneously in frontal scalp and pharyngeal leads, no occasion was witnessed when it was observed first in the pharyngeal leads.

Records VII and VIII were obtained from two patients with expanding pituitary tumours. In both instances there was evidence of extrasellar extension of the tumour. The first patient (Record VII) showed in addition to the typical X-ray appearances, optic atrophy and symptoms of hypopituitarism. The second patient (Record VIII) was a man of 41 with severe acromegaly of six years' duration who had diabetes, progressive blindness, behaviour disorder and a radiogram showing depression and erosion of the floor of the pituitary fossa suggesting a tumour. In both cases records were obtained from two bipolar pharyngeal leads. Although both these records are disturbed by artefacts, both show the presence of theta rhythm of moderate amplitude and fair rhythmicity. In the second case (Record VIII) some irregular delta activity is also apparent. Neither of these rhythms can be seen in the records obtained from scalp leads.

Discussion.

In view of the variability of electrode placement in this technique the term "pharyngeal" is preferable to "basal." Consideration of the anatomical relationships of the nasopharynx suggests that electrodes planted there are as near to the mid-brain, pons, medulla and inferior aspects of the temporal lobes as to the hypothalamus. The assumption that such electrodes are recording the activity from specific areas is certainly not justified. For the following reasons the single pharyngeal electrode is, in our opinion, of little value. First, when used as a unipolar lead, such a lead is as diffuse as that attached to the ear lobe. Second, as Dawson has pointed out (Personal Communication), the technique cannot be used for the location of a bilaterally synchronized rhythm if only three channels are available. For when two channels are connected in series, the common electrode being pharyngeal and the other two on either side of the skull, it follows that in the case of bilaterally synchronous rhythm, phase reversal for the waves will be seen inevitably at the common

electrode. Record IV demonstrates this for the wave and spike discharge in the case of antero-posteriorly placed electrodes also.

The introduction of two pharyngeal electrodes encounters many technical difficulties, but records can be obtained from them. Although the records can be obtained most easily with spike electrodes implanted in the mucous membrane, such electrodes may not be without danger, and if this technique were to find a place in clinical electroencephalography, the contact electrode, although more difficult to apply, would be preferable. The advantage of two pharyngeal electrodes lies in the fact that they can be used independently of reference either to scalp leads or to earth. Further, by their use time relations for discharges between scalp over the vault and pharynx can be observed. Potential changes recorded between two such electrodes, placed closely together, are necessarily small.

The records obtained from normal persons with normal EEGs showed no alpha rhythm activity from the pharyngeal leads. In four cases low voltage beta rhythm (20-25 c./sec.) was seen consistently. Visual attention had no effect on this rhythm. In normal persons an insignificant amount of theta rhythm was observed from the double pharyngeal leads. On the other hand, in both cases of pituitary tumour a marked theta rhythm of moderate voltage dominated the record, and in the second case this theta rhythm was not observable in records obtained from scalp leads. This suggests that the pharyngeal electrode technique may be of value in recording the early changes from basal lesions before such lesions produce theta rhythm in the cerebral cortex.

With the triangle electrode technique and a single pharyngeal electrode we have repeated Jasper's observation of phase reversal for the waves of the *petit mal* discharge at the pharyngeal electrode, but, as already indicated, this does not provide evidence of the basal origin for the *petit mal* attack. When two pharyngeal electrodes were used and independent recording made from them and from scalp electrodes, the wave and spike discharge sometimes appeared first in the frontal cortex and sometimes simultaneously there and in pharyngeal leads. Despite many observations in a case with very frequent discharges no occasion was observed when the discharge appeared first in the pharyngeal leads. This patient is an idiopathic epileptic of many years' duration who, some months before the observations, had suffered a severe head injury. However, the wave and spike complexes were bilaterally synchronous in character, therefore conforming to the idiopathic epileptic picture. On numerous occasions discharges of delta wave activity were seen from the frontal scalp leads first, later from the pharyngeal leads and occasionally persisting from the latter after their disappearance from the former. These findings, there-

fore, indicate that in the case investigated extensively the *petit mal* attack did not have a site of origin nearer to the pharyngeal leads than to the scalp leads but usually the reverse. Further, that in so far as a spatial focus can be assumed for the origin of the wave and spike discharge, such a focus has itself a variable location. This suggests that it is unlikely that the *petit mal* attack is dependent upon the discharge of any one group of neurones.

SUMMARY.

(1) The electrical activity of the brain has been recorded from single and double pharyngeal electrodes on twelve subjects, normal and abnormal.

(2) The advantages of two pharyngeal electrodes are emphasized.

(3) In the normal subject the rhythmical activity seen from such electrodes is of beta frequency (20-25 c./sec.) and of low voltage. This activity is independent of alpha rhythm activity.

(4) In an epileptic's EEG, wave and spike discharges were recorded simultaneously and independently from pairs of pharyngeal and scalp electrodes. These discharges appeared either first in the frontal scalp pair or simultaneously in the latter and the pharyngeal pair of electrodes.

The pharyngeal electrodes were constructed by Mr. P. St. John Loe, and we are indebted to him and to Mr. J. Theobald, technical assistants, for their help in these experiments. It is also a pleasure to record our indebtedness to Mr. V. E. Negus, F.R.C.S., for his advice and also to Professor S. Nevin for his advice and support.

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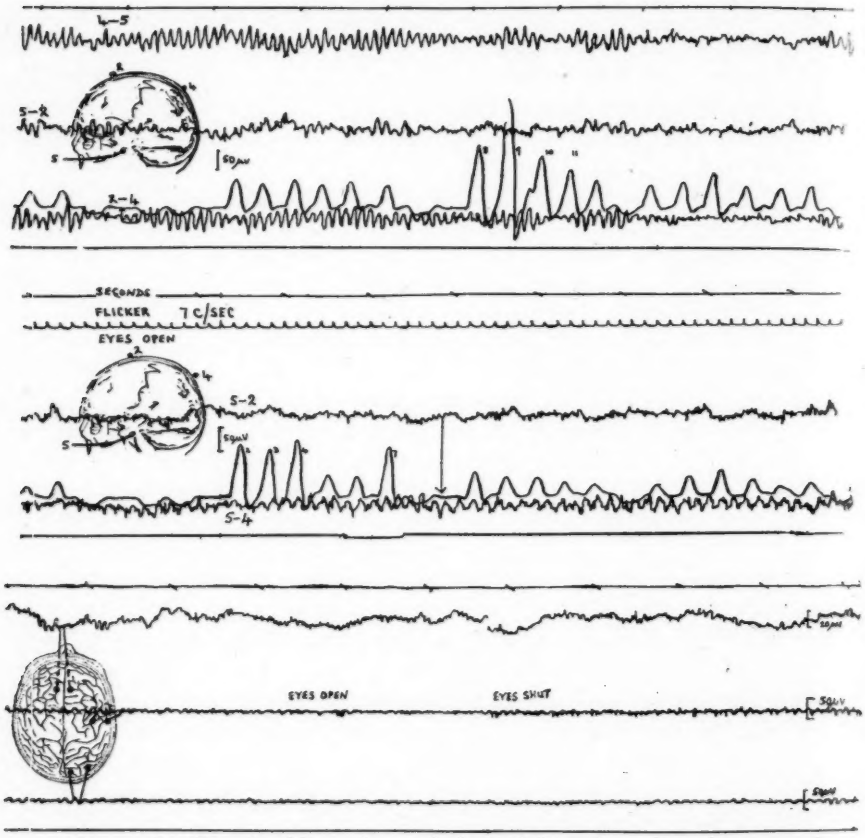
NOTE.—Owing to an error, the blockmaker, with a view to greater clarity of reproduction, has inked in the EEG tracings. Apologies are offered for the artificial appearance occasionally produced thereby.

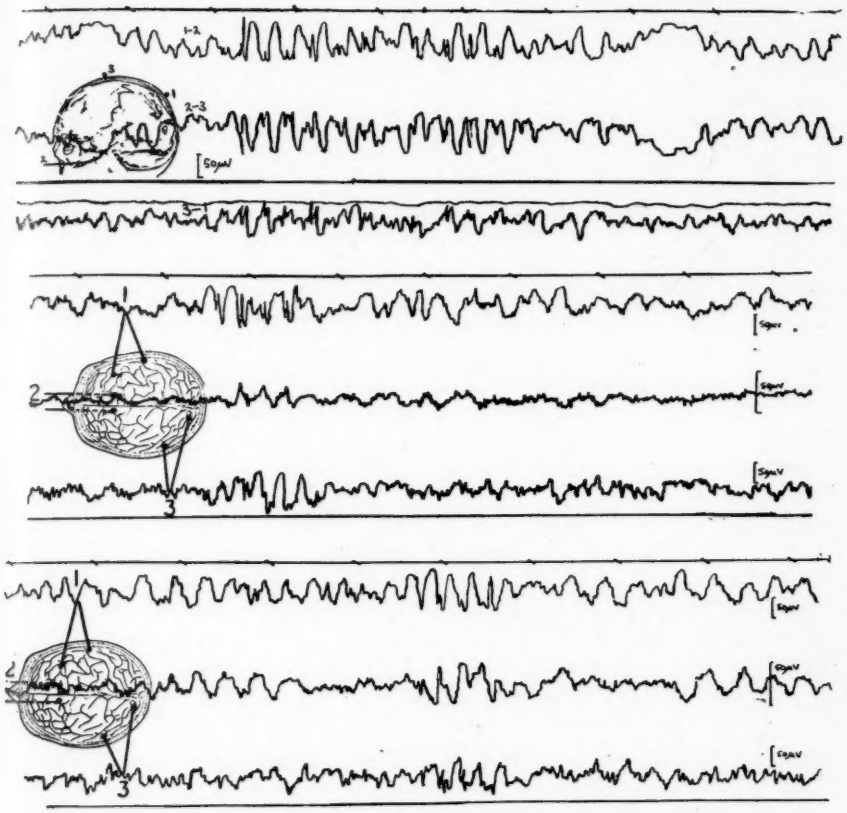
DESCRIPTION OF RECORDS.



RECORD I.—Normal subject. A record obtained from three electrodes arranged in a triangle, the apex of which is at the base. The middle channel shows absence of rhythmical activity compared with the two outside channels. This central channel is recording between the base and the frontal region.

RECORD II.—Normal subject. A record obtained from electrodes in the same positions as in I showing the response to a flickering light with frequency of 7 c/sec. shone on the eyes. The lower channel shows the cells of the occipital cortex following at this frequency. The middle channel again shows no rhythm of this frequency. This indicates that the basal electrode is not picking up the activity of the visual system.

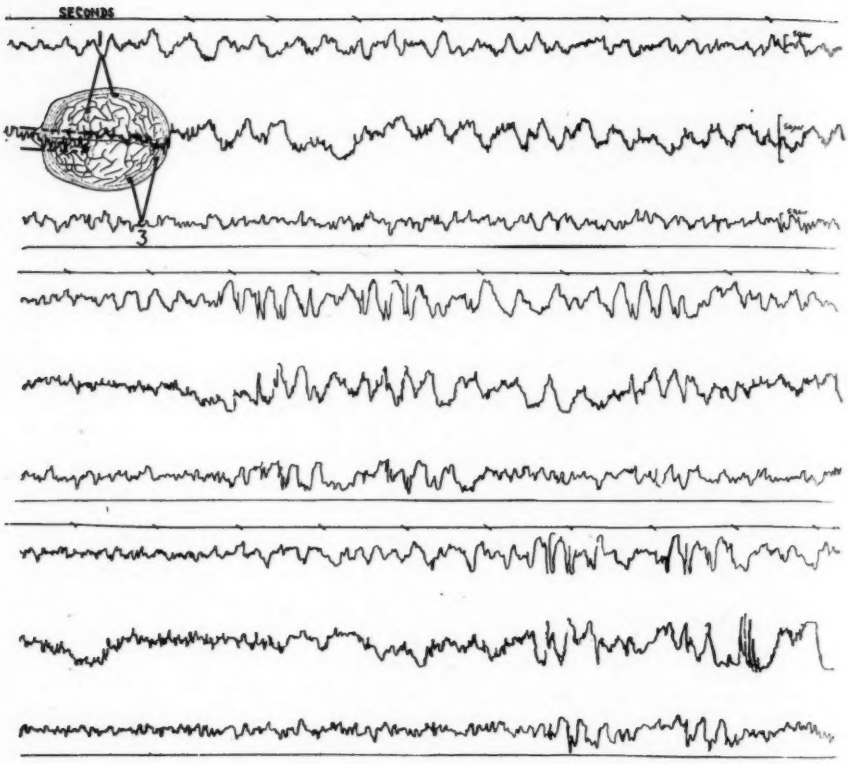
RECORD III.—Normal subject. Record obtained from paired pharyngeal electrodes, paired temporal (scalp) electrodes and paired occipital (scalp) electrodes. All rhythms are small, since paired scalp electrodes are closely spaced to compare with pharyngeal electrodes. Eye closure has no effect upon rhythm (mainly beta) from pharyngeal electrodes.



RECORD IV.—Epileptic subject. Record obtained from electrodes arranged as in I and II; demonstrates that spike and wave complexes locate to the basal electrode by phase reversal (*see* 1 - 2, 2 - 3). The third channel (3 - 1) records the activity of the cortex.

RECORD V*a* AND *b*.—Epileptic subject. Two pharyngeal electrodes were used, the activity from which is recorded in the second channel of each tracing. In these records the channels are recording independently—No. 1 from the right frontal cortex, No. 2 from the pharyngeal electrodes and No. 3 from the left occipital cortex. The amplification in the second channel is much greater than that in the other two.

In (*a*) a short burst of wave and spike activity is seen *appearing first* in the right frontal leads. After a delay of nearly half a second, it is seen in the pharyngeal leads. On the other hand in (*b*) occurring later, the onset of wave and spike activity appears simultaneously in leads from frontal cortex and pharynx.

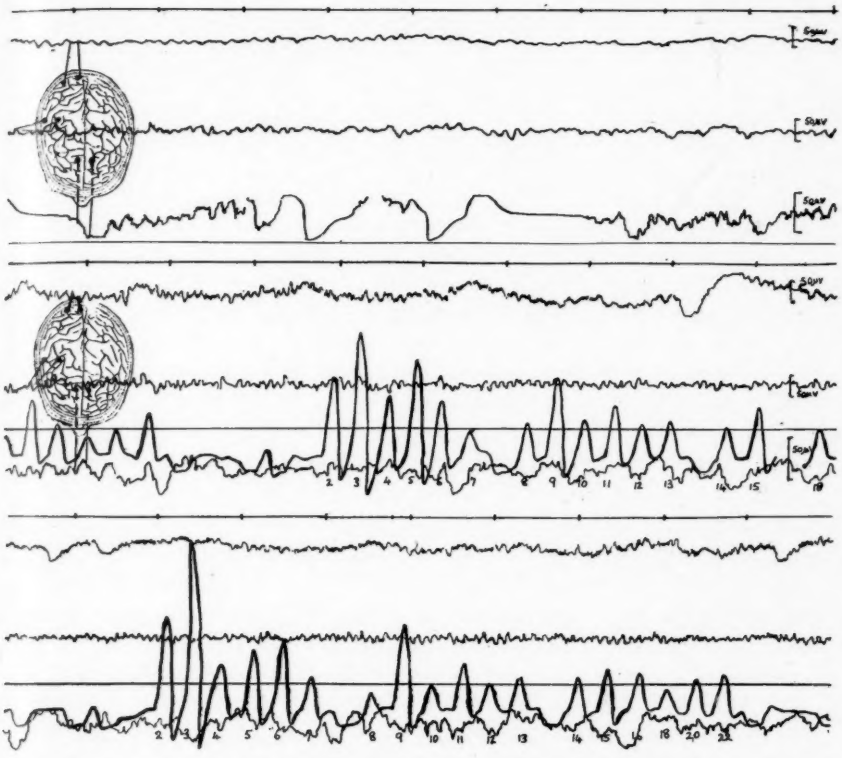


RECORD VI*a*, *b* AND *c*.—This record was taken from the same epileptic subject as in Record V with the electrodes in the same positions.

In (*a*) irregular delta activity starts in the frontal cortex, later involves the pharyngeal electrodes and persists in the latter after diminishing at the cortical electrodes.

In (*b*) a wave and spike attack starts in the frontal region first, later appearing at the pharyngeal electrodes.

(*c*) shows another wave and spike attack, on this occasion appearing simultaneously at cortical and pharyngeal electrodes.



RECORD VII.—Expanding pituitary tumour (*see* text). Record obtained from paired pharyngeal and paired scalp electrodes. From the latter, activity at 7-8 c/sec. is seen; from the pharyngeal electrodes rhythmical 6 c/sec. activity is apparent, when the tracing is free from movement artefact.

RECORD VIII.—Expanding pituitary tumour (*see* text). Record obtained from paired pharyngeal and paired scalp electrodes. Automatic frequency analysis of activity obtained from pharyngeal electrodes is superimposed and shows excess activity at 2-3 c/sec. and at 5-6 c/sec. rhythm. Both frequencies are apparent in the primary record but not in those from scalp leads.

THE DISTRIBUTION OF SYMPATHETIC FIBRES IN THE BRACHIAL PLEXUS IN MAN.[1]

BY

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PERIPHERAL vascular complications associated with abnormal ribs and soft tissue relations at the cervico-thoracic junction have, in general, been attributed either to pressure on the subclavian artery or to irritation of the vasomotor fibres in that portion of the brachial plexus which is subjected to pressure, stretch or angulation. This paper is concerned with the distribution of the sympathetic fibres in the plexus, with particular reference to their possible implication in the production of such circulatory disturbances. The observations were made on normal dissecting-room and post-mortem material and on the brachial plexus of a patient with cervical rib in whom, during life, vascular symptoms were the predominating clinical feature.

The neurogenic theory appears to have originated with Gordon (1901), who suggested that cervical ribs might exert their harmful vascular effects by disturbing the inferior cervical sympathetic ganglion and its branches to the lower roots of the brachial plexus, all of which were shown by dissection to be intimately related to the vertebral extremity of the abnormal rib. Todd (1912, 1913) also attributed the vascular symptoms to pressure on sympathetic fibres, but he placed the lesion in the lower trunk of the plexus at the point where the rib impinged on it. No attempt was made, however, to explain why only a small proportion of the cases of cervical rib showed vascular disturbances until Telford and Stopford (1931) suggested that it was due to the variable arrangement of the sympathetic fibres in that part of the plexus subjected to distortion. This opinion was based on the histological examination, in eight dissecting-room subjects, of that part of the lower trunk which is related to the 1st rib. They reported that sympathetic fibres were usually scattered among the somatic fibres, with "a slight tendency for them to reside principally around the circumference of the trunk"; in one specimen,

[1] This work was assisted by a grant from the National Health and Medical Research Council of Australia.

however, the sympathetics were said to form a distinct and separate bundle in the inferior part of the trunk. Such a discrete bundle would, they believed, be more vulnerable to irritation from a cervical rib, while the infrequency of this arrangement would explain why the vascular complications appear only occasionally.

This hypothesis was tested by Blair, Davies and McKissock (1935) when they examined, post mortem, the distal part of the plexus in a case of cervical rib in which there had been marked vascular effects during life. The fibres comprising the grey rami were observed to disperse among the somatic fibres immediately on entering the 7th and 8th cervical roots. The proximal half of the 1st thoracic nerve was not examined. In the distal half of this nerve and in the lower trunk of the plexus myelinated and unmyelinated fibres were intermixed and there was no tendency for the latter to be concentrated at the periphery. They concluded that the vascular effects were the result of an "irritative" lesion of the sympathetic fibres caused by an endoneuritis of the lower trunk.

The neurogenic theory has been consistently criticized, and much clinical evidence has now accumulated (Lewis and Pickering, 1934; Eden, 1939; Falconer and Weddell, 1943; Walshe *et al.*, 1944) to demonstrate that the vascular symptoms are the effect of pressure on the subclavian artery, though there is still a difference of opinion as to the mechanical factors responsible for the pressure. In arriving at this conclusion attention has been focused on the positive evidence favouring the vascular theory, while irritation of sympathetic fibres has been rejected as an ætiological factor without considering whether there were any confirmed peculiarities about their arrangement which would predispose them to irritation.

Despite the detail already provided in the literature, there are still some points relating to the sympathetic outflow to the upper limb which require clarification. Telford and Stopford examined only that part of the plexus in contact with the 1st rib, their identification of sympathetic fibres depended solely on fibre-structure and they did not indicate what proportion of the sympathetic fibres to the limb was contained in the isolated bundle described by them to be in direct apposition to the rib. Blair, Davies and McKissock also relied on the degree of myelination for the identification of sympathetic fibres. Axford (1928) has provided a comprehensive account of the macroscopic features of the cervical sympathetic chain, while the studies of Harman (1900), Johnson and Mason (1921), Juba (1930), and the recent detailed investigations of Sheehan (1941) and Pick and Sheehan (1946) have provided valuable

information relating to the histological structure of the rami passing to the plexus. So far as can be determined, however, the post-ganglionic fibres to the arm have not been traced from the ganglia into and along the plexus to a level beyond the 1st rib. Such a study requires serially-sectioned material and the micro-dissection of cleared and stained specimens.

Material and Methods.

Clinical.—A search of the literature has revealed only one account of a patient presenting vascular disturbances as a predominant feature of cervical rib in whom the brachial plexus was obtained post mortem and examined histologically (Blair, Davies and McKissock, 1935). A second case prompted the investigation which is the subject of this paper. For convenience the case-history, post-mortem findings and histological observations will be reported under the section entitled "Clinical Observations."

Anatomical.—Observations were made on 30 dissecting-room and 4 post-mortem specimens. In these the brachial plexus, the related sympathetic chain and the rami communicantes were carefully dissected from the intervertebral foramina to a point just beyond the outer border of the 1st rib. The surface of the plexus which was applied to the rib was suitably marked. The spinal nerves were then sectioned at the intervertebral foramina, the sympathetic chain severed at appropriate levels and the plexus divided just beyond the rib. The structures were removed *en masse* without disturbing the normal arrangement and were further examined in one of three ways:—

(1) The rami communicantes were traced by micro-dissection into and along the nerve roots until their dispersal among the somatic fibres prevented any further examination by this method.

(2) Specimens were stained with eosin, cleared in cedar wood oil, and the rami traced under the dissecting microscope.

(3) The individual structures in 6 dissecting-room specimens were suitably marked and arranged to permit their identification in section. The tissue was fixed in formalin, embedded, serially sectioned transversely at 15 μ and the sections stained with hæmatoxylin and eosin. The post-mortem specimens were fixed in Flemming's solution, embedded, serially sectioned at 5 μ and stained with iron hæmatoxylin and light green. The sections were enlarged on a micro-projector, drawn and the diagrams assembled in serial fashion to reconstruct the macroscopic arrangement. In this material it was possible to trace the fibres from the sympathetic ganglia into and along the roots of the plexus. The structure of the rami was further investigated histologically in another 6 specimens.

Anatomical Observations.

General.

The term "root" has been applied to that portion of a spinal nerve between the intervertebral foramen and the point of participation in the plexus formation.

(1) The plexus was formed in the customary manner, by the 5th, 6th, 7th and 8th cervical and 1st thoracic nerves in all specimens; in 13 a small contribution was received from the second thoracic nerve.

(2) The inferior cervical and 1st thoracic sympathetic ganglia were either fused or separated by a short, stout neck; the term "stellate" is considered appropriate for the combined ganglia and will be used in this sense throughout the text.

(3) The fibre-structure of the rami varied greatly. The four types described by Pick and Sheehan (1946) were identified histologically but could not be distinguished macroscopically.

Type I: White ramus composed entirely of myelinated fibres of large calibre.

Type IIA: Characteristic grey ramus composed entirely of non-myelinated fibres.

Type IIB: Grey ramus heavily peppered with fine myelinated fibres less than 3 μ in diameter.

Type III: Mixed ramus containing non-myelinated and large myelinated fibres in varying proportions. In the present series these were either intermingled indiscriminately or arranged as two separate groups, the separation being accentuated in some specimens by a fibrous septum.

On approaching the nerve root the mixed rami usually split into numerous finer radicles which effected a separation of the two types of fibre, though even in the finer radicles some mixing occasionally persisted.

Sympathetic neurons were observed in two rami, each of which passed to the 8th cervical nerve. Woollard and Weddell (1935) also reported them in rami to this nerve, while a wider distribution has been recorded by Skoog (1947).

(4) All roots of the plexus carried post-ganglionic sympathetic fibres to the periphery.

(5) The 5th and 6th cervical nerves received single or multiple (2 to 4) grey rami: (i) directly from (*a*) the middle cervical ganglion, (*b*) the superior cervical and stellate ganglia for the 5th and 6th roots respectively, and/or (*c*) the intervening sympathetic trunks, and (ii) indirectly from the stellate ganglion by way of the plexus which accompanies the vertebral artery cranially.

These sympathetic fibres represented only a very small proportion of those destined for the limb, and by the time they reached the upper trunk of the plexus they were widely dispersed among the somatic fibres. These nerve roots did not receive myelinated fibres from the sympathetic trunk.

(6) The 7th cervical nerve received 1 to 3 grey rami from the stellate ganglion and, in most cases, additional fibres from the vertebral plexus. Pick and Sheehan's (1946) observation that these rami are of Types IIA and IIB, with the former predominating, was confirmed.

(7) The 8th cervical and 1st thoracic roots received post-ganglionic fibres from the stellate ganglion. The communication which the 2nd thoracic nerve may send to the 1st (Cunningham, 1877; Herringham, 1886; Harman, 1900; Todd, 1912*b*; Kuntz, 1927, and Sheehan, 1933) carried additional sympathetic fibres to the latter nerve from the 2nd thoracic ganglion. No post-ganglionic fibres were observed passing directly to the 1st thoracic root either from the 2nd thoracic ganglion or from the 3rd in the manner described by Kirgis and Kuntz (1942).

(8) Woollard (1931) reported that "the caudal roots of the plexus receive a greater number of post-ganglionic fibres," and, in a later paper with Weddell (1935), presented evidence that "over twice the number of sympathetic fibres were contributed to the 8th cervical compared with any of the other roots." The relative sympathetic contribution to each root, based on the cross-sectional areas of the rami, is at present under investigation, but preliminary observations confirm that the bulk of the sympathetic fibres to the limb travel in the lower trunk. In some specimens, however, the contribution to the 1st thoracic exceeds that to the 8th cervical, while a substantial number of sympathetic fibres also accompanies the 7th cervical distally.

The 8th Cervical and 1st Thoracic Nerves.

The 8th cervical nerve inclined downwards, forwards and outwards to cross the 1st rib. It was joined, medial to the inner margin of the bone, by the 1st thoracic root, which was directed obliquely upwards and outwards to effect the union. It was therefore the lower trunk of the plexus and not a free nerve root which crossed the rib; the former was either in direct contact with the bone or elevated above it by scalenus medius fibres and/or the subclavian artery. The fibres facing or applied to the bone, however, were those originally contained in the infero-lateral portion of the 1st thoracic root, though these were replaced by 2nd thoracic fibres when this nerve sent a contribution to the plexus. Occasionally some rotation of the trunk was brought about by the slope of the rib and the direction taken by the anterior fibres of the scalenus medius; when this occurred fibres originally occupying the postero-inferior aspect of the 8th cervical nerve came to face, or were brought into contact with the bone.

The 1st thoracic nerve was usually composed of a single funiculus and the 8th cervical of several bundles. Above the rib the lower trunk was composed of several funiculi engaging in plexus formations, though in two specimens the fibres were contained in a single bundle at this level. In some specimens the plexus formations were confined to two separate groups, each representing the nerve root from which it was originally derived; in others, neighbouring funiculi of each group had already intercommunicated, thereby effecting an early exchange and mixing of fibres from different roots.

Unipolar neurons, frequently in large numbers, were seen (six specimens) extending distally along the nerves for distances up to 1 cm. beyond the intervertebral foramina—in two specimens these were not continuous with the neurons of the posterior root ganglion (*see* fig. 1). These aberrant sensory nerve cells were more common in the 8th cervical. The presence of such cells in the posterior roots has been frequently reported (Quain, 1895; Poirier and Charpy, 1901; Piersol, 1919; Duncan and Crocker, 1939; Peters, 1940; Morris, 1942; Cunningham, 1943; Gray, 1946), but, to the author's knowledge, there has been no previous reference to them extending distally into the spinal nerve beyond the intervertebral foramina. Skoog (1947) illustrates and describes aberrant ganglion cells in the 8th cervical nerve, but it is not clear from his account whether or not these extended outside the intervertebral foramen.

The Rami Communicantes to the 8th Cervical and 1st Thoracic Nerves.

General.—The number of rami to each root varied from one to six; each was composed of a single or of several funiculi. Those for the 8th cervical were usually confined to the proximal pole of the ganglion, and those for the 1st thoracic nerve to the distal, though on occasions this arrangement was reversed. The rami arose either from the anterior or posterior surface of the ganglion, but usually from the latter. In general, they were either short and thick or long and thin; those for the 1st thoracic were usually of the former variety and those for the 8th cervical of the latter.

Emerging from the ganglion the rami proceeded either medially or laterally, though most, regardless of their fibre-composition, were directed laterally and entered the spinal root obliquely.

A ramus either entered a single root with or without preliminary branching, or divided and was distributed over adjacent nerve roots.

Fibre structure.—Most of the rami to the 8th cervical root were of

Types IIA and B (grey), but a mixed ramus, or rami, in which heavily myelinated fibres comprised up to one-third of the cross-sectional area was present in approximately 10 per cent of the specimens (fig. 2). Rami of this type entered the root distal to the others. No pure white rami (Type 1) were seen. The heavily myelinated fibres in the mixed ramus were traced centrally as far as the intervertebral foramen; owing to the termination of the sections at this level, it could not be ascertained whether they then entered the anterior or the posterior root. A comparison of the arrangement, however, with that obtaining further distally suggested that pre-ganglionic fibres may leave the cord above the 1st thoracic level, which Sheehan (1941) and Pick and Sheehan (1946) claim to be the cranial limit of the outflow. Such a finding, however, is consistent with the observations of Siemerling (1887), Harman (1900), Herring (1903), Gagel (1928), Wrete (1934), Arnell (1937), and Kirgis and Kuntz (1942), while Ray, Hinsey and Geohegan (1943) found that the 8th cervical was the highest spinal root to give sympathetic effects on stimulation.

The rami to the 1st thoracic nerve were predominantly of the mixed (1 or 2) and grey (2 to 4) types; pure white rami were rare. The most distal ramus was usually mixed and transmitted the bulk of the heavily myelinated fibres passing between the nerve and the ganglion; this agrees with the observations of Axford (1928) and of Pick and Sheehan (1946). This mixed ramus usually emerged from the lateral aspect of the ganglion and was, because of its distal point of entry into the nerve, longer than its fellows.

Distribution of the Sympathetic Fibres in the Lower Trunk and its Roots of Origin.

The rami entered the contiguous margins and the adjacent anterior surfaces of the converging nerve roots. This feature is illustrated in articles by Harman (1900) and Sheehan (1933), but is not mentioned in their text. As a result the post-ganglionic fibres for both roots were directed to the angle outlined by their fusion. Incorporated into somatic funiculi they then proceeded into the substance of the lower trunk either centrally or more superficially beneath its anterior face. On no occasion did a ramus enter the infero-lateral aspect of the 1st thoracic nerve which would eventually carry its fibres into direct relationship with the 1st rib.

The most medial (or proximal) rami joined the nerve within a few millimetres of the intervertebral foramen, and, with one exception, the most lateral (or distal) joined it proximal to the formation of the lower trunk. In the exceptional case, a long grey ramus coursed laterally to

join the upper surface of the lower trunk in the region of the 1st rib—it was therefore separated from the bone by the full thickness of the trunk.

On joining the epineurium of the nerve root some fibres of the ramus passed proximally, some distally, and others immediately entered a funiculus. Many of the centrally directed fibres remained in the epineurium as far as the intervertebral foramen, while others were rapidly absorbed in the funiculi containing somatic fibres. Only occasionally did the distally-directed fibres remain in the epineurium for more than a short distance. Other than the exception referred to, no independent sympathetic bundle was observed in the lower trunk at the level of the 1st rib.

On entering a funiculus the sympathetic fibres proceeded as a group to the central axis or beneath the perineurium for a variable distance before being dispersed among the somatic components. The 1st thoracic root was usually composed of a single funiculus partitioned by fine septa, and the fibres of the rami joining it were so gradually scattered that, by the time nerve root union had occurred, only a small proportion had reached that section of the trunk which was passing into direct contact with the rib. The 8th cervical root, on the other hand, was usually composed of several funiculi between which the sympathetic bundles coursed before finally terminating in the manner outlined. This, together with the funicular intercommunications, contributed to a more rapid and widespread dispersal of the fibres. The intraneural behaviour of the sympathetic fibres was therefore such that they were irregularly scattered, singly or in small groups, through the lower trunk at the level where it crossed the rib, though they predominated in the antero-superior portion of the trunk.

An arrangement which brought sympathetic fibres more directly into association with the bone occurred when the 2nd thoracic nerve contributed a branch to the plexus. This branch carried sympathetic fibres derived from the 2nd thoracic ganglion (and occasionally from the 3rd). Though these fibres represented only a very small proportion of those reaching the lower trunk, they passed to its undersurface and were still confined to, though scattered over, the lower 3rd of the trunk as it passed over the rib.

Clinical Observations.

Case report.—G. S., Army No. V6543, a male aged 50 and left-handed, was a sergeant in the armed forces with thirty-six months' service. The symptoms were of ten years' duration. In the winter of 1933 he first noticed that during the day

the four fingers of his left hand became white, cold and stiff and that, though he could bend his fingers quite strongly, his hand was rendered useless. There was no pain. When in bed at night "the circulation" returned and the fingers turned a "pinky blue." These attacks occurred daily during that winter and he was treated, non-operatively, at a public hospital for Raynaud's disease. Every winter subsequently these attacks returned with increasing severity. In the winter of 1943 they were accompanied by deep "bone" pains in the shoulder, arm, forearm and fingers while the patient also complained of superficial pain extending down the inner aspect of the limb as far as the hand. When in bed these attacks subsided. The right hand had a tendency towards blueness but there were no symptoms referable to this limb. There was no ulceration of the fingers at any time. The patient was admitted to the 115th Australian General Military Hospital in May 1943.

Examination June 1, 1943.—The only signs and symptoms were those referable to the left arm.

All movements were slightly weaker on the left than on the right and this impairment was maximal in the hand but not in any particular group of muscles. There was very slight wasting of the interossei and a slight flattening of the thenar eminence. There was no wasting of the forearm 10 cm. below the medial humeral epicondyle while 15 cm. above this point the left arm was fuller than the right by a quarter of an inch. The arm-jerks were normal and equal on the two sides. No objective sensory impairment could be detected. There was no involvement of the cervical sympathetic field.

The four fingers were pale blue and cold—these changes extended as far proximally as the middle of the metacarpals. The pulse on the left side was weaker than on the right and was not changed with elevation or retraction of the shoulders. Blood-pressure: Right 145/90; Left 108/72. Examination of the supraclavicular region revealed a palpable rib on the left side. No pulsations of the subclavian artery were visible.

X-ray examination revealed (i) hypertrophy of the transverse processes of the 7th cervical vertebra with a left cervical rib at least 5 cm. in length; (ii) a normal rib on the right; (iii) scoliosis of the cervico-thoracic junction with right-sided wedging of the body of the 7th cervical vertebra together with well-marked arthritic changes in the area—particularly on the right side; (iv) spondylitic lipping in the mid and lower cervical vertebræ.

Operation June 8, 1943 (Major H. Trumble).—The brachial plexus was exposed through a supraclavicular incision, the long thoracic, suprascapular and phrenic nerves retracted and the scalenus anterior divided. The subclavian artery and lower trunk of the plexus were acutely angulated over the rib and the former was narrowed at this point. There was no arterial dilatation proximal or distal to the site of narrowing. The cervical rib was carefully resected. There were complete articular spaces at the transverse process of the 7th cervical vertebra and between the anterior extremity of the cervical rib and the upper surface of the 1st rib in the region of the scalene tubercle.

Immediately following the operation the colour returned to the hand, the fingers lost all stiffness and the pain disappeared except in the region of the trapezius. The immediate relief of symptoms was a striking feature. The convalescence was uneventful until eighteen days after the operation when the ankles and feet became swollen and the patient showed symptoms of cardiac distress. Two days later the heart had increased markedly in size, the cervical veins were swollen, there was a small amount of fluid at the base of the left lung and the patient was very distressed. The subsequent events and electrocardiograph readings were consistent with a coronary sclerosis. The patient died thirty-two days after the operation.

Post-mortem examination.—A post-mortem examination was made at which I was given the opportunity of dissecting both supraclavicular regions. The following observations were made:—

Bone: There was no abnormality on the right. On the left the stump of the cervical rib was located posteriorly between the 7th and 8th cervical roots.

Vascular: The subclavian veins were normal and no difference could be detected between the two sides. The right subclavian artery was normal. The left was narrowed for about 15 mm. where it had been angulated over the rib. This segment was removed for examination. No other portion of the vascular tree was examined.

Neural: The composition of the brachial plexus was identical on the two sides despite the absence of a cervical rib on the right. It was formed by the 5th, 6th, 7th and 8th cervical and 1st thoracic nerves. The largest root was the 7th cervical and the next largest, the 8th. The 1st thoracic was very small (approximately one-third the usual size) and ascended vertically to join the lower margin of the 8th cervical nerve well medial to an impression left by the rib on the undersurface of the lower trunk of the left plexus.

The left stellate ganglion was larger and softer than its fellow on the right (this appeared to be due to œdema) and was slightly more congested. These changes were attributed to operative interference. The rami to the 5th, 6th and 7th cervical nerves were not traced into the plexus. The 8th cervical and 1st thoracic nerves received 6 and 4 rami respectively and these were rapidly incorporated into the nerve roots. The impression left on the undersurface of the lower trunk of the plexus by the abnormal rib was still visible; there were no isolated sympathetic bundles in the epineurium at this level.

The plexus and adjacent sympathetic trunk on both sides were removed and prepared for histological examination in the manner previously described. The tissue was fixed in formalin, block stained in hæmatoxylin and eosin and serially-sectioned transversely at 15 μ. The sympathetic fibres were traced, as in the dissecting-room material, into and along the plexus.

Microscopic Observations.

Normal side: The sympathetic fibres were distributed in the manner previously described for the dissecting-room material and the arrangement calls for no further comment. Neurons were observed in the rami to the 8th cervical nerve while unipolar neurons in large numbers extended along the 1st thoracic nerve for approximately 8 mm. beyond the intervertebral foramen.

Involved side: At the site of formation of the lower trunk the 8th cervical nerve was composed of a single funiculus and the 1st thoracic of one major and two satellite bundles (fig. 4). The latter were rapidly absorbed into the inferior aspect of the 8th cervical bundle so that the fibres of the two roots were soon contained in a single funiculus. This then commenced to divide so that at the level of the rib impression the trunk was multi-funiculated while some mixing of 8th cervical and 1st thoracic root fibres had occurred.

One grey and 3 mixed rami joined the inner margin of the 1st thoracic root which was directed vertically upwards. The mixed rami (one large and two fine) entered the root distal to (i.e. above) the grey. Owing to the small size of the thoracic root the sympathetic fibres were unevenly scattered through it by the time root union occurred; despite its smaller size it carried, so far as could be determined by cross-sectional areas, its normal quota of sympathetic fibres. This meant that in comparison with the fibre-ratios customarily obtaining, there was a relative increase in the sympathetic components.

The single funiculus of the 8th cervical nerve received 3 grey and 3 mixed rami; the post-ganglionic fibres greatly exceeded in number those to the 1st thoracic nerve. The rami joined its anterior face and the contained fibres were rapidly scattered through it. When the 1st thoracic funiculi were absorbed into the inferior portion of the 8th cervical funiculus the arrangement was such that sympathetic fibres were irregularly scattered, singly or in small groups, through the single bundle comprising the lower trunk. By the time the rib impression was reached further fibre-mixing had occurred, which had been aided by the subdivision of the original funiculus; no concentration of sympathetic fibres could be detected in that sector of the trunk which had been in contact with the abnormal rib.

There was a perivascular infiltration of small round cells in the epineurium of the lower trunk, and the stellate ganglion was congested (fig. 5); this acute reaction was attributed to the operation. The epi and perineurium at the site of pressure from the abnormal rib were slightly thicker than at the corresponding level on the opposite side. The nature of this thickening suggested that it was of long standing. There was, however, no endoneuritis and no detectable morphological evidence of permanent damage to nerve fibres.

The structure of the wall of the subclavian artery at the site of the constriction was normal.

Conclusions.—The investigation revealed no anatomical peculiarities about the distribution of the sympathetic fibres in the plexus which would have exposed them more than their somatic neighbours to irritation or pressure by the cervical rib. The minor impairment of somatic motor and sensory functions, together with the absence of any detectable morphological evidence of permanent damage to nerve fibres, points to a vascular basis for the vascular symptoms. The subclavian artery was acutely angulated over the abnormal rib and narrowed at that site; the arrangement was such that the weight of the dependent arm would have accentuated the angulation. These changes appeared to be sufficient to obstruct the circulation of the limb, but only to such a degree that it required cold weather and a dependent arm to precipitate vascular complications at the periphery. The immediate relief of symptoms following removal of the rib supported such a reconstruction, while the immediate amelioration of symptoms would have been unlikely in the presence of chronic morphological changes induced in the vessel or brachial plexus.

There remains the possibility, however, that mechanical stimulation of only a few of the scattered sympathetic components in the lower trunk, or of the periarterial sympathetic plexus about the subclavian artery, may have set up a source of chronic irritation at the site of stimulation. This may have been responsible for exciting widespread vascular reflex effects at the periphery with the production of vascular symptoms. If this were the case, then it must be assumed that the sympathetic components were physiologically more susceptible to stimulation than the somatic components which surrounded them.

Conclusions and Summary.

(1) The distribution of the sympathetic fibres in the brachial plexus has been described with particular reference to their possible implication in the production of vascular complications in cases of cervical rib. The observations were made on normal dissecting-room and post-mortem material and on the brachial plexus of a patient with cervical rib, in whom vascular symptoms were the predominating clinical feature during life.

(2) The 8th cervical and 1st thoracic nerves joined before reaching the 1st rib, and the lower trunk thereby formed crossed the bone usually as a multi-funiculated structure, but occasionally as a single bundle. Funicular divisions and intercommunications in the trunk resulted in a rearrangement of the nerve fibres which, in some cases, involved intermingling of adjacent 8th cervical and 1st thoracic fibres. Though the extent to which this occurred varied from specimen to specimen, the somatic elements which were most directly related to the rib were derived solely from the 1st thoracic root.

(3) Preliminary studies have demonstrated that the majority of the sympathetic fibres to the limb travel in the 8th cervical and 1st thoracic nerves, with a substantial number also accompanying the 7th cervical. The rami contributing post-ganglionic fibres to the lower trunk of the plexus entered the contiguous aspects of the anterior faces of the converging nerve roots, and as the fibres proceeded distally they were directed into the substance of the trunk (either centrally or beneath its anterior face) and not to its undersurface. In only one specimen did a ramus join the lower trunk directly, but in this instance the site of entry was separated by the full thickness of the trunk from the rib.

After a very short course in the epineurium of the spinal nerve the bundles comprising the rami joined somatic funiculi through which the sympathetic fibres were then dispersed. This dispersal was well advanced by the time root union occurred to form the lower trunk, where further fibre mixing was effected both by the intrafunicular movement of fibres and by funicular plexus formations. As a result of these changes the sympathetic fibres were widely but irregularly scattered, singly or in small groups, through the lower trunk at the level where it crossed the rib, though the bulk of them were observed to reside in the antero-superior portion of the trunk; the small proportion of fibres dispersed over that sector which is applied to the bone reached it via rami which had joined the 1st thoracic nerve. With the one exception referred to there was no isolated sympathetic funiculus at this level, nor were there any

anatomical peculiarities about the distribution of the sympathetic fibres to the plexus which would expose them to pressure or irritation or would provide an explanation for the infrequency of the vascular complications of cervical rib.

(4) The arrangement was such that if sympathetic fibres react to mechanical stimuli more readily than their somatic neighbours, it is because they are physiologically more susceptible and not because they are anatomically more exposed. In any event, the 1st sympathetic fibres to respond under such conditions should be those reaching the trunk over the 1st thoracic nerve, and if it be assumed that these have a peripheral distribution which is related to that of the somatic fibres of that root, then sympathetic effects should be evident in the 1st thoracic field. Numerous observers, however, have commented on the vulnerability of the index finger and radial half of the hand which are rarely included in the field of the 1st thoracic nerve. The possibility remains, however, that the local disturbance induced in a few fibres may result in more widespread reflex effects at the periphery.

(5) When the 2nd thoracic root contributed to the plexus its fibres were directed into that portion of the lower trunk passing into direct apposition with the rib. In no instance, however, did the associated sympathetic fibres remain so confined or were they sufficiently numerous to invalidate the conclusion that the sympathetic fibres are not, by virtue of any concentration or position in the trunk, rendered more susceptible to mechanical stimuli.

(6) Observations indicate that the sympathetic outflow from the cord may extend as high as the emerging 8th cervical roots.

(7) Rami frequently transmitted both myelinated and non-myelinated fibres to the nerve roots forming the lower trunk of the plexus; for this and other reasons it was not possible to identify "grey" and "white" rami macroscopically. Though the most distal ramus joining a nerve root was commonly mixed or white in type, this was not invariably the case.

(8) Only two cases have been reported in which vascular complications were the predominating clinical feature of cervical rib and in which the involved brachial plexus was examined post mortem. Blair, Davies and McKissock attributed the vascular effects in their case to an endoneuritis of the lower trunk which resulted in irritation of the sympathetic fibres.

In the case reported in this paper there was no endoneuritis and no detectable morphological evidence of permanent damage to nerve fibres. Furthermore, the sympathetic fibres were widely and irregularly scattered, singly or in small groups, through the funiculi comprising the lower

trunk at the level where it crossed the abnormal rib. The subclavian artery was acutely angulated over the cervical rib and narrowed at that site; the arrangement was such that the weight of the dependent arm would accentuate the angulation. These changes appeared to be sufficient to obstruct the circulation of the limb, but only to such a degree that it required cold weather and a dependent arm to precipitate vascular complications at the periphery. The immediate relief of symptoms following removal of the rib supported such a reconstruction of events, while the immediate amelioration of symptoms would have been unlikely in the presence of chronic morphological changes induced in the vessel or plexus.

(9) The observations reported in this paper do not support the belief that the vascular complications of cervical and abnormal thoracic ribs are directly due to a neurogenic factor in the form of irritation of, or pressure on, exposed sympathetic fibres at the site where the plexus is related to the abnormal rib.

The findings, however, do not exclude the possibility that mechanical stimulation of a few of the scattered sympathetic components in the lower trunk, or of the periarterial sympathetic plexus about the subclavian artery, may set up a source of chronic irritation at the site of stimulation which might excite widespread vascular effects at the periphery with the production of vascular symptoms. Where this occurs in the absence of impairment of somatic motor and sensory function, it must be assumed that the sympathetic components are physiologically more susceptible to stimulation than the somatic components which surround them.

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LEGENDS FOR FIGURES.

FIG. 1.—Photomicrograph of a transverse section of the 1st thoracic nerve root distal to the intervertebral foramen illustrating (i) unipolar neurons and (ii) the entrance of a grey ramus and the subperineurial spreading of its fibres.

FIG. 2.—Photomicrograph of a transverse section of a ramus to the 8th cervical nerve containing many heavily myelinated nerve fibres of large calibre.

FIG. 3.—Photomicrograph of a transverse section of a nerve root illustrating the manner in which a grey ramus may enter and pass to the centre of a funiculus before its fibres are dispersed through the bundle.

FIG. 4.—Photomicrograph of a transverse section of the converging 8th cervical and 1st thoracic nerve roots from the involved side in patient G. S. to illustrate the relative size of the two roots. The 1st thoracic (T.1) is composed of one major and two satellite bundles—one of the latter has just fused with the undersurface of the large 8th cervical funiculus. Rami are shown passing to the interval between the two nerve roots prior to joining the antero-inferior surface of the large 8th cervical funiculus.

FIG. 5.—Photomicrograph of a transverse section of the stellate ganglion from the involved side in patient G. S. illustrating the extent of the congestion present.

PLATE VII

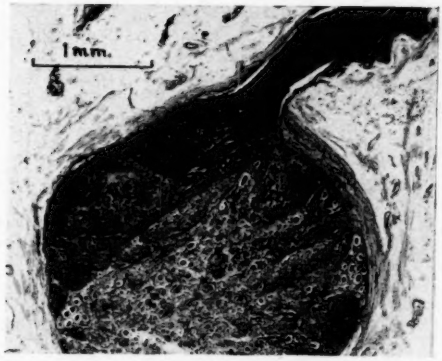

FIG. 1.

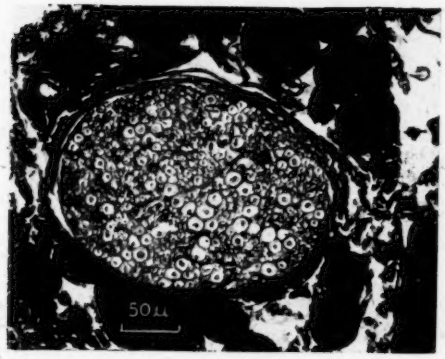

FIG. 2.

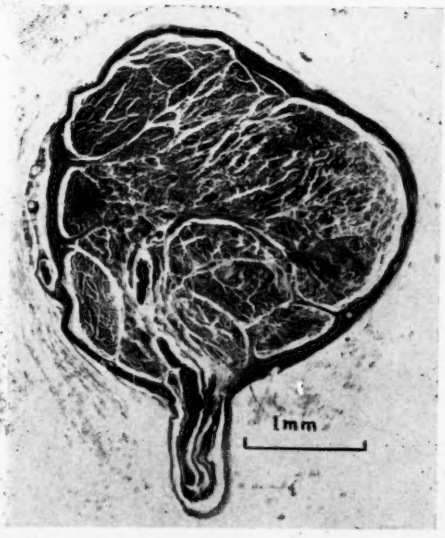

FIG. 3.

To illustrate article by Sydney Sunderland.

PLATE VIII

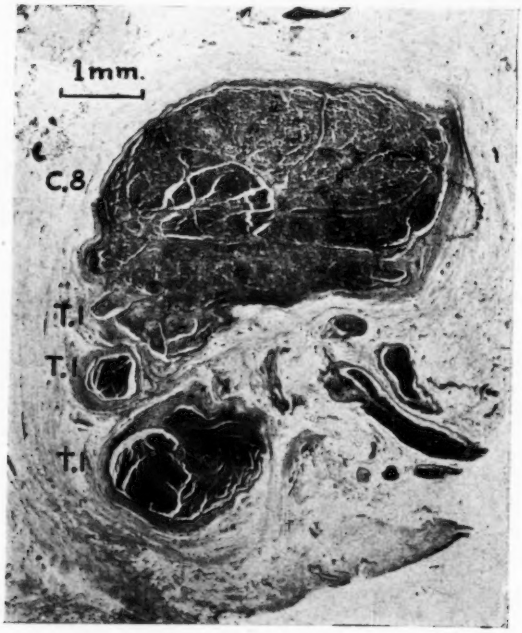

FIG. 4.

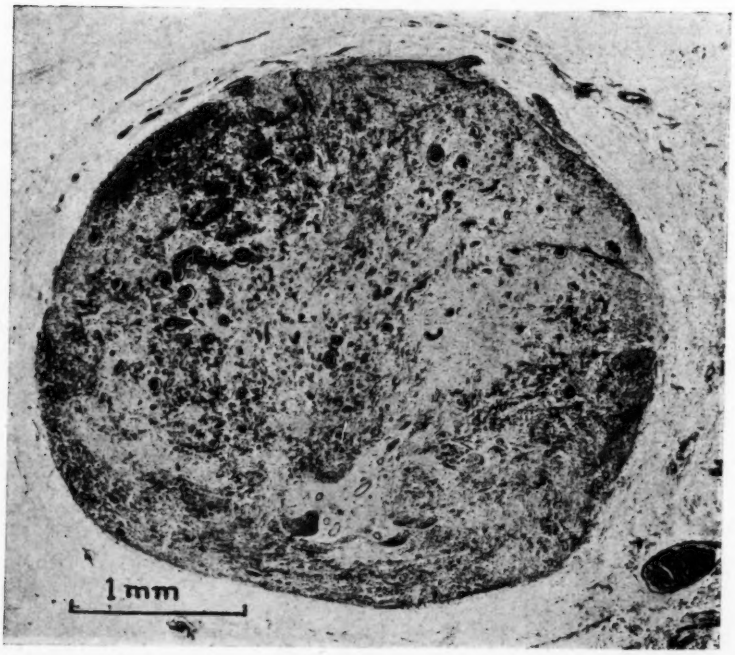

FIG. 5.

To illustrate article by Sydney Sunderland.

Notices of Recent Publications.

Harvey Cushing—a Biography. By John F. Fulton. 1946. Pp. 754. Oxford: Blackwell. Price 30s.

All must agree that Professor Fulton's Life of Harvey Cushing is something of which he can well be proud. Few biographers can have commenced their tasks with so many documents of one kind or another from which to select. We may be sure that unless he had restricted himself very severely this "Life" would have run to several volumes; for Cushing, the universal collector, had kept numerous unusually lively diaries illustrated by that skilful pencil which was so great an asset to him all his life.

The early years of Cushing's life are remarkably well told in these chapters. It was a part well worth doing at some length because there was so much evidence in the form of letters to his father and mother and in those to his friends that it gives a vivid picture of a doctor's home in a middle Western city (Cleveland) in the '80s and '90s. So rapidly have the U.S.A. grown that sidelights on the doings of an unusually gifted young man born into an educated family is of interest to a larger audience than a medical. Cushing early showed that tireless drive which was to be his characteristic, that intense dislike of rivalry, that daemon that made him crash ahead regardless of other people's feelings or wishes. It is odd in its way that anyone who was as sensitive as Cushing (and no one who knew him well could doubt for a moment the sincerity of his pity for those in pain or distress nor doubt the warmth of his friendship for those whom he liked) could be so unaware of another point of view. We may be sure that he was very well aware of that but chose, when it suited him, to disregard them. Cushing's own need was always so much greater than the other man's. This universal law of human nature he used with more success than most of us.

Professor Fulton in this book gives a very clear account of Cushing's early experimental work and of his clinical contributions. His criticisms of the former are admirably just but yet critical. In the main the defect of the latter was that they simplified pathological processes and their clinical effects too much. There was little of an A. N. Whitehead, with his "seek simplicity and suspect it" in Cushing. Professor Fulton has little to say about this. Cushing was often criticized in Britain for not giving enough credit to other forerunners, unless they were happy old American surgical gods like W. W. Keen or great men not recently neurologically very important like, say, Durante. Cushing's blindness to Horsley was, it could be said, subconsciously necessitated by his own needs. It must be admitted that his dislike of certain of the older generation of British Neurosurgeons was exalted by the cruel witticisms that were thrown back at him. It was a bad business on both sides. Cushing's inability to recognize the importance of Sherrington when both he and Sherrington were young is not very surprising. Cushing was then a self-confident youngster just returned from a year in Bern and not very ready to see anything very impressive in Englishmen. Nor was Sherrington universally greeted as the great man that he undoubtedly was until some years after Cushing first knew him.

For his outstanding act of courage he will always be remembered, the dedication of himself to the surgery of the nervous system as a pure specialism in the earliest years of this century. Many must have told him that it was madness to commit his fortunes and those of his wife-to-be to so supposedly threadbare an existence. He might so easily have failed. His success was due entirely to his own efforts, to a strength of character that made it possible for him to follow an ideal that had nothing to do with the fleshpots and the eating of bread. We have to thank the fearless leadership of Cushing for the establishment of neuro-surgery as a self-supporting specialism.

Cushing's positive achievements were not only numerous but great. He rescued the surgery of the central nervous system from an operative technique unsuited to it. The new one was not, it is true, entirely Cushing's own invention. What Cushing did was to apply the extremely cautious, painstaking methods that he had learned from the masters, Halsted and Kocher. It was a technique that did not come naturally to a surgeon, it was a discipline that had to be acquired. The casual visitor to the operating room would be more bored than impressed by it but in reality it was a connoisseur's technique. There were trivial observers who thought that Cushing was an ungifted operator. This was wildly untrue, for not only had he the body balance of the athlete but he had an artist's hands as his pencil sketches so clearly show.

His dominant characteristic was his dedication of himself to his work and its improvement. Book collecting was his only real hobby and he cut himself off from social distractions with an almost puritanical zeal. The honesty of his periodic reports on work done cannot be doubted. He imposed these reviews on himself as an obligation. They were his means of discovering what progress he was making and they led him forcibly, as it were, to understand the anatomical lay-outs and the natural history of brain tumours. He knew little about histology, it was Percival Bailey who filled in that side of the picture for him. But Cushing's contribution proved to be the greater for he pursued the question of what a tumour that occupied such and such a situation and had this or that appearance did to the patient who had it. When this knowledge was added to Bailey's histology there resulted a new confidence, an added firmness in grappling with cases. And of course his work on pituitary tumours remains monumental. We can fairly call it that even though we disagree with many of his beliefs on pituitary functions. It was through his experience with these adenomas in particular, although not because of that alone, that Cushing became so interested in visual field work. It will not be forgotten that he raised field taking, through his associates, to a pitch of detailed excellence never achieved before and only rarely equalled since. The great labour that it entails forbids it to the lazy.

Cushing had a sincere belief in discipleship as the only way of learning. The handing out of useful "tips" was, he thought, dangerous. He had himself been under Halsted's jurisdiction for eight years at Baltimore, so he could hardly be expected to countenance short courses in and short cuts to knowledge in neuro-surgery. And he was right, for, when all is said and done, Harvey Cushing remains one of the Master Surgeons.

The biography gives a clear picture of the development of Cushing's love of books, which dated from the early days at Baltimore with Osler and Welch, and of his many friendships amongst bibliographers in many countries, notably with Klebs. This was a really important side of Cushing's nature and no one is better fitted to speak of it than Professor Fulton whose work in that field is so well known. It rounded out the figure of the man and brought him many interesting friendships that his ordinary scientific work would have denied him.

Reading of the visits that he made over here almost yearly, the important lectures that he gave, the medical functions that he attended, the great men that he met, make us regret the passing of an age, the like of which we ourselves shall never see again. The Europe that he so eagerly and gaily visited lies in ruins; where once were held national and international gatherings of great splendour, the bats fly. In that way Cushing's story is mixed with the cultural history of Europe and is a continuation of and a contrast to the simpler background of Ohio in his youth.

It may be that Professor Fulton's choice of emphasis has erred a shade towards the more showy side of Cushing's great performance. Cushing's work was not flashy. The long periods of toil, self-searchings and self-criticism that ran all through his life are not so well described as the public occasions which, after all, are only a small part of any but a politician's life. A man can be over-dramatized.

GEOFFREY JEFFERSON.

Diseases of the Nervous System. By W. RUSSELL BRAIN. Third Edition. 1947. Pp. 987. Oxford Medical Publications. Price 37s. 6d.

The appearance of the third edition of this well-established textbook will be widely welcomed. Amongst textbooks on its subject in the English language which seek to cover the entire field of clinical neurology it is quite outstanding. It is what it purports to be, primarily a clinical textbook containing a balanced account of the maladies with which it deals, their features and course, their ætiology and their pathology. The needs of clinical diagnosis are comprehensively dealt with, and the introduction of anatomical and physiological matter is determined by the clinical usefulness these subjects have.

Thus it shows that harmony between the different elements which go to the making up of a clinical textbook of the first rank. We still lack a full dress modern textbook of neurology of the scope and calibre of the textbooks of Gowers or of the English translation of Oppenheim, since, unhappily, Kinnier Wilson's premature death left his work incomplete and unrevised. Nevertheless, within its scope and for the class of reader for whom it is intended, Dr. Russell Brain's book may be warmly recommended as an admirably written and faithful presentation of clinical neurology.

A Textbook of Clinical Neurology. By I. WECHSLER. Sixth Edition. 1947. London: W. B. Saunders Co. Price £2 2s.

The sixth edition of this popular textbook continues to live up to its title by providing an adequate exposition of clinical neurology, and by refraining from crowding this out by those sections—so commonly irrelevant and uncritical—on anatomy and physiology that characterize many neurological texts in the country of its origin.

Dr. Wechsler's book is outstanding amongst American neurological texts in that he has not been afraid to keep it clinico-pathological in its emphasis.

A minor criticism is, perhaps, that he has not in this edition brought his text quite up to date. The sections on rib pressure syndromes, on the pathology of cerebral vascular lesions, on Ménière's syndrome, on spinal cord injuries, on the cerebellar syndrome, and on cerebral aneurysms, to name but a few, might all with advantage be recast and made to do justice to recent additions to knowledge and modern viewpoints.

Abnormal Psychology. A Clinical Approach to Psychological Deviants. By JAMES D. PAGE. 1947. Pp. xvii, 441. New York and London: McGraw-Hill Book Company. Price 20s.

This is a textbook of psychiatry for undergraduates, and is written on a very simple level. It is readable, lucid and interesting, and is to be commended as a well-written introduction to the subject for the medical student. It is clear that the author is well read in modern contributions to psychiatry in the European as well as the American literature, and has exercised good critical judgment in their exposition. The result is a balanced presentation, without undue stress being laid on the teachings of any one school.

The Neocortex of Macaca Mulatta. By G. VON BONIN and P. BAILEY. Illinois Monographs in the Medical Sciences. Vol. 5, No. 4. 62 plates. Urbana, Ill.: University of Illinois Press. Price $4.

It is to be doubted whether this beautifully produced and illustrated monograph is free from the now known defects of cortical cytoarchitectonics of the Brodmann-Vogt order.

Indeed the text is almost as hard to correlate with the figures as in the Vogt contributions to the subject, and when read by itself lacks those qualities of clarity and definiteness that are so necessary. Further, the individual variations from specimen to specimen, so clearly brought out by Lashley and Clark, and so essential to an assessment of current teaching, are not adequately dealt with. Yet, almost despite themselves as it were, the authors do contribute the too slowly growing realism in the matter of cortical cytoarchitectonics. Thus, they allow that the so-called suppressor bands do not correspond with named cortical areas, that the Betz cell is a virtually indefinable entity, and is of a distribution that defies generalization. The "strip" known as 4S they cannot differentiate.

It seems, therefore, that the falsely precise parcellations of the cortex which we have allowed ourselves to accept, and upon which we have built so much and so rashly, are slowly dissolving, and with them much also of the cortical physiology based upon them. We still await a truly scientific cortical cytoarchitectonics. The way to it has been clearly indicated by Lashley and Clark.

The Post-natal Development of the Human Cerebral Cortex. Volume III. The cortex of the three-month infant. By J. LE ROY CONEL. 1947. Harvard University Press. Pp. 160 and 104 full page plates. Price 12 dollars 50 cents.

The earlier volumes of this ambitious monograph were reviewed in *Brain* in 1939 and 1942, and it is a pleasure to welcome the third volume of the series. The earlier volumes dealt with the human cerebral cortex at birth and at one month and described neurons without Nissl granules and for the most part without neurofibrils. At three months there is considerable progress towards maturity in the primary afferent and efferent areas of the cortex. In most areas the cortex has now increased in width, an increase due chiefly to growth in layers 1 and 3. The granular layers show least increase and in many areas none at all. The enlargement of the cortex both in thickness and in area results in wider spacing of the neurons which themselves have undergone only slight enlargement.

The chromophil granules in the cytoplasm now begin to assume the size and shape of Nissl granules especially in the Betz cells of the motor cortex, and in the larger pyramidal cells in the primary reception centres for touch, hearing and sight. The differentiation of neurofibrils from the rows of argyrophilic granules which precede them is carried a stage further. At the age of one month neurofibrils were only found in the Betz cells of the limb and trunk areas. At the age of three months there is little advance beyond this stage in the frontal lobes, except in the motor area for the head, but neurofibrils have also become differentiated in a few of the largest pyramidal cells in the primary reception areas of the parietal and occipital lobes. Myelination has also progressed considerably from the one-month stage.

These and other evidences of maturation of the neuron are described in detail both as to character and distribution and are illustrated by beautiful camera lucida drawings. The scholarship of the work and the beauty of format are the same as in the earlier volumes. But the present volume has a special interest for all those interested in the neurology and psychology of childhood, as it appears to provide an anatomical substratum for the transition of the child's behaviour during the first three months of life from simpler to more complex reflexes, and to explain the postponement to a still later age of behaviour of a more voluntary character. We hope that Professor Conel will be able to continue this series with studies of the cerebral cortex at later age periods.

Pathology of Tumours. By R. A. Willis. Butterworth & Co., London, 1948. Pp. 1044 with 500 illustrations. Price 63s.

A new textbook on tumours is greatly needed as the English speaking world has, for many years, been entirely dependent on Ewing's book, which though in many respects authoritative, has in successive editions lost something of its original character.

Dr. Willis' textbook is based on his own experience at the Alfred Hospital in Melbourne and the result is a freshness and individuality of approach which are very welcome.

The first 200 pages are filled with discussions on the nature, origin and spread of tumours, in which much of the recent work on cancer research is surveyed. The rest of the book is taken up by descriptions of the various tumours, which are classified according to their type rather than their situation. The description of tumours of the nervous system is based on the examination of a series of 436 tumours from the neuro-surgical clinic of the Alfred Hospital and shows evidence of the author's special interest in this branch of pathology. In his simplified classification of the gliomas, he follows the lines suggested by Scherer's work, and the influence of Nicholson's teaching that very few types of tumour arise from "cell rests" is also evident. In this we would agree with him, with the reservation that some of the rarer forms of glioma, such as those found in association with neurofibromatosis and tuberous sclerosis may have a developmental basis. On ependymal tumours he is essentially conservative and accepts neither Bailey and Cushing's *ependymoblastoma* nor Kernohan's *myxo-papillary ependymoma.* On his classification of the endotheliomas we reserve judgment. It seems unlikely that the common type in which vessels are scarce, and the highly vascular type in which vessels are formed by the tumour cell are derived from the same type of cell, nor do we agree that cerebellar hæmangioblastomas are not true tumours, with considerable powers of growth. In distinguishing between solitary and multiple neurofibromas he follows

lines already familiar from the writings of Penfield and del Rio Hortega, but concedes that "neurilemmomas" may occur in von Recklinghausen's disease and that solitary neurofibromas may occur. Those with a larger experience of neurofibromatosis know that the type of tumour which he calls "neurilemmoma" is that most usually encountered as a multiple tumour of nerve roots, an instance of his exception becoming the rule. Dr. Willis' dogmatism on this and other points is stimulating to the thoughtful reader, who must often wish that he would state the reason for his views more fully.

Specialists in other systems of the body will, no doubt, have similar criticisms to make, but it must be granted that the author shows a remarkably wide knowledge of his subject, and has covered a large field in a very competent manner. The book must be regarded throughout as expressing the author's own opinion, which is not necessarily definitive and often has a conservative trend.

The illustrations are excellent, and the large bibliography with which each chapter concludes will be of great value to those seeking further information.

Mongolism and Cretinism. By CLEMENS E. BENDA. Wm. Heinemann, London. 1947. Pp. xv, 310. Price £1 5s.

The author presents the results of eight years of investigation into the pathology and ætiology of mongolism. They are put down in an orderly, but not very readable way; and, as is often the case with individual contributions, there is a considerable lack of proportion. The hæmatological and biochemical investigations, the work of Dr. E. M. Bixby, are listed in full and form an addition to our knowledge of the condition. The pathological investigations are also given in detail; but there is a dearth of good photomicrographs, and the presentation conforms to the author's theories. In this section most of the space is devoted to the endocrine glands, failure of whose functions is presumed to play a predominant role. It is clear, however, from the study of the other organs, that the histology of the mongol is universally abnormal, and that no common factor emerges.

Physical characteristics and mental development receive less thorough treatment. Although anthropometric figures are listed in full, only a minimum of measurements has been recorded. The chapter on the mental development of the mongol is very weak. The results of 329 intelligence tests on 132 mongols are presented graphically, but no details of the methods are given. There is no discussion of qualitative psychological abnormalities, apart from passing note on the mongol's emotional lability, powers of mimicry and love of music. The author is apparently aware of the limitations of the concept of mental age as a measure of mental development, but still writes as if he supposed that the mongol with a mental age of 3 had the same mental processes as a normal child of that age.

The clinical and pathological data are presented to support the theory that the primary lesion is in the anterior pituitary, and mongolism is a congenital acromicria. The evidence is insufficient. For instance, the author is so unfortunate as to discover that there is an excess of acidophils present in the pituitaries of his subjects, and has to presume that current theories of hypophyseal function and histology are wrong.

Two final chapters on prevention and treatment reflect the author's views on ætiology and pathology.